AUGUST 1953
VOL. VIII NO. 2

Circulation

A JOURNAL of the AMERICAN HEART ASSOCIATION

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Circulation
A Journal of the American Heart Association

AUGUST 1953
VOL. VIII NO. 2

Rheumatic "Activity" as Judged by the Presence of Aschoff Bodies in Auricular Appendages of Patients with Mitral Stenosis

I. Anatomic Aspects

By J. P. Decker, M.D., C. Van Z. Hawn, M.D., and S. L. Robbins, M.D.

Left auricular appendages from 183 patients, removed at operation for mitral stenosis, have been studied with regard to presence of Aschoff bodies and endocardial thrombi. An over-all incidence of Aschoff lesions of 40 per cent was found. There was a significant decrease in Aschoff lesions in the presence of thrombosis. The occurrence of Aschoff bodies in the appendages is correlated with the findings in the remainder of the heart in autopsied cases.

THE DEVELOPMENT of methods for the surgical correction of rheumatic deformities of the mitral valve has afforded an opportunity for the examination of the left auricular appendage which is removed at the time of operation. It is thus possible to study cardiac tissue in living patients and to correlate simultaneously clinical and pathologic observations.

The microscopic anatomy of the auricle has been described by Gross.[1] The auricular appendage is similar to the auricle, differing chiefly in that the appendage has a thinner wall and presents many irregular pockets and trabeculations. Rheumatic endocarditis involving the mural endocardium of the left auricle is a well-recognized entity,[1-4] but Aschoff lesions in the auricular appendage have not been described except in connection with studies similar to the present one, although Von Glahn stated that superficial auriculitis which is responsible for the development of the MacCallum patch may extend into the first portion of the appendange.

Others have reported the pathologic findings in auricular appendages removed at the time of surgical intervention for the correction of mitral stenosis of rheumatic origin. Pinniger[5] noted the presence of Aschoff nodules in 10 of 15 left auricular specimens. Kuschner, Ferrer, Harvey and Wylie[6] report finding Aschoff bodies in 4 of 11 auricular appendages. Biörck, Winblad and Wulff[7] found Aschoff lesions in 7 of 18 specimens. Sabiston and Follis[8] noted the presence of Aschoff bodies within the endocardium or myocardium of the auricular appendage in 32 of 43 cases.

The Aschoff lesion is generally regarded as the most characteristic finding of rheumatic inflammation in the heart, affording a useful criterion, when properly characterized morphologically, for the microscopic recognition of rheumatic inflammation. The specificity of the lesion has been questioned,[9] but most authors[10-13] agree that the lesion is a specific one indicative of activity of the rheumatic process. It has, therefore, been selected as the sole cri-

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This study was supported in part by a grant from the National Heart Institute.

terion for the evaluation of rheumatic activity in the present study. The morphology of the Aschoff body has been well described by Gross and Ehrlich[10] and, in general, their criteria for its identification have been followed in this study. Briefly, it is characterized by evidences of disorganization in the fibrous tissue in which it occurs, the collagenous fibers showing swelling, eosinophilia, granular degeneration or necrosis. The degenerative change is accompanied by a rather special sort of inflammatory infiltrate in which large, irregular cells with ragged edges, basophilic cytoplasm and one or more vesicular nuclei with "owl-eyed" nucleoli are present. In addition, various other less characteristic inflammatory cells may be present, for instance, lymphocytes, plasma cells and histiocytes.

Only lesions presenting these features have been identified as Aschoff bodies in this study, except that a few minimal lesions possessing some, but not all, of the features described have been included. The basic alteration occurring in the Aschoff lesion has long been thought to occur in the collagenous fibers. The Aschoff or "owl-eyed" cell usually has been considered a tissue histiocyte of a sort peculiar to cardiac tissues. Recently, however, it has been suggested[13] that some, at least, of the myocardial Aschoff bodies may have their origin in a primary injury to cardiac muscle fibers and that the giant cells are derived from the damaged muscle cells.

Up to July 1, 1952, 223 left auricular appendages had been examined in the pathologic laboratories at the Boston City Hospital and the Peter Bent Brigham Hospital. After careful clinical appraisal, none of the patients from whom the specimens were taken was thought to have active rheumatic carditis at the time of operation. The histologic findings are presented in 183 appendages. Forty specimens have been excluded from the study for the following reasons: seven were excluded because the amount of tissue available for examination was considered inadequate for proper evaluation, 10 because the lesions found were equivocal and no agreement could be reached regarding their significance, and 23 more were rejected because clinical data were either not readily available or inadequate for proper appraisal of clinical activity.[14]* The 183 auricular appendages were studied for the presence of Aschoff bodies. The appendages were also studied for the presence of fresh or organized endocardial thrombi and the presence of thrombosis correlated with occurrence of Aschoff bodies.

Twenty-two patients came to autopsy at the Boston City and Peter Bent Brigham Hospitals. The sections of the hearts in these cases have been reviewed and the presence or absence of Aschoff lesions correlated with the findings in the auricular appendages. An additional series of 11 rheumatic hearts in the general autopsy material at the Boston City Hospital was also studied with particular reference to the correlation of rheumatic activity in the left auricular appendage and in the remainder of the heart.

Occurrence of Aschoff Lesions

An approximation of the frequency with which Aschoff bodies were encountered in the appendages has been indicated by a system of grading. Specimens graded as showing 1 plus activity were those in which only one or two recognizable Aschoff lesions were seen (fig. 1). The appendages showing the largest numbers of Aschoff bodies, sometimes as many as 10 or 12 in a single low-power field, were graded 3 plus (fig. 2). Specimens showing intermediate degrees of activity were graded 2 plus.

The Aschoff lesions seen in this study were located within the endocardium or, more commonly, in the loose-structured subendocardium (fig. 3). No lesions were seen which could be interpreted as properly myocardial in location. The auricular appendage presents such a convoluted pattern that lesions which are separated from the main cavity of the appendage may still be related to an isolated pocket of endocardium. The lesions seen in the subendocardial tissues correspond mostly to the reticular and mosaic forms described by Gross and Ehrlich[10] (fig. 4). Those occurring in dense fibrous tissue often appeared compressed. Some

* Eight of the 23 rejected cases showed Aschoff bodies, an incidence comparable to that in the remainder of the series.

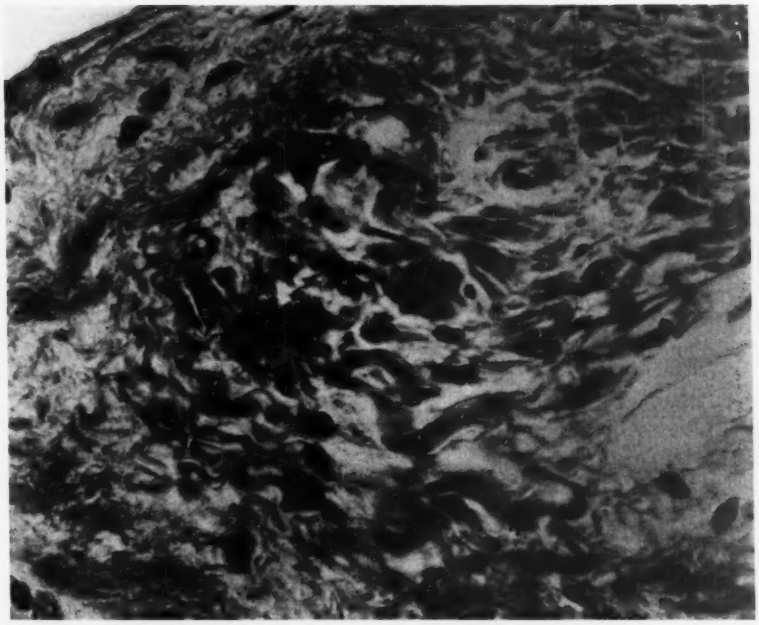

FIG. 1. One of two endocardial Aschoff lesions in the auricular appendage of autopsied case 2. Note the double nucleated cell. One plus activity.

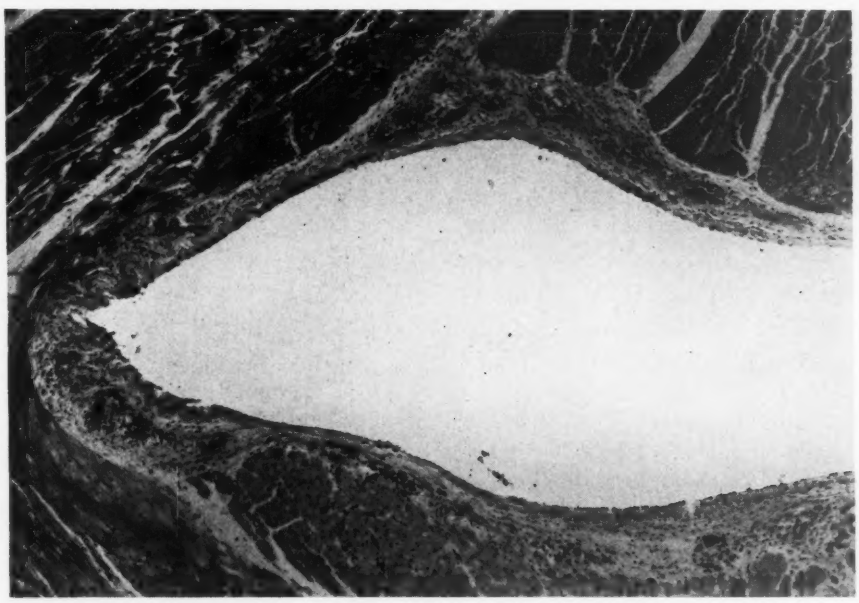

FIG. 2. Thirteen subendocardial Aschoff lesions in a low-power view. Three plus activity.

lesions of this sort show an alignment of Aschoff cells along swollen collagenous bundles suggestive of the auriculitis seen in the left auricle (fig. 5). Other features seen include both diffuse and focal endocardial fibrosis, a finding also noted by others who have examined similar material. Focal lymphocytic collections were frequently present in the endocardium, myocardium and epicardium. Their relation to

FIG. 3. Subendocardial Aschoff lesions showing numerous basophilic cells.

rheumatic disease is not clear. It seemed that they were frequently associated with endocardial thrombosis.

Aschoff bodies were found in 83 of the 183 auricular appendages, a total incidence of 45.3 per cent (table 1). Despite the fact that the biopsies from the two hospitals were interpreted by different observers, except for the doubtful cases which were seen by all, it is interesting that there is close agreement in the results reported from the two sources, the incidence of

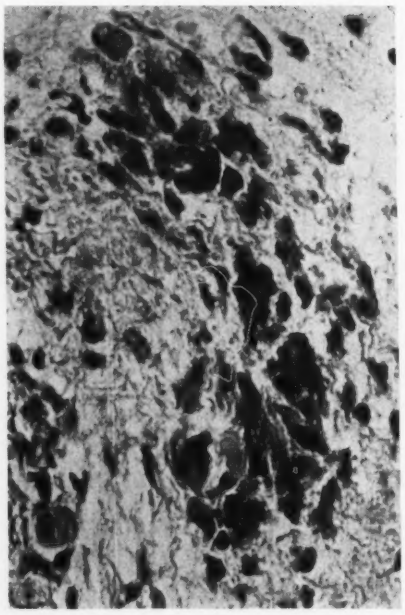

FIG. 4. Large subendocardial Aschoff lesion showing characteristic cellular infiltrate and alteration in fibrous tissue.

FIG. 5. Two subendocardial Aschoff lesions from appendage of autopsied case 1. Considerable endocardial fibrosis is present.

Aschoff lesions being 43.9 per cent in the specimens from the Boston City Hospital and 45.8 per cent in the larger series at the Peter Bent Brigham Hospital. Two and 3 plus activity have been separated from 1 plus or minimal activity, as the higher grades of activity may have a somewhat greater significance as will be pointed out in connection with the autopsied cases. Twelve of the 41 appendages from the Boston City Hospital showed considerable endocardial fibrosis. One of these showed Aschoff lesions.

The incidence of rheumatic activity in the auricular appendages in the present study conforms generally to the published observations of Pinniger,[5] of Kuschner, Ferrer, Harvey and Wylie[6] and of Biörck, Winblad and Wulff.[7] The incidence of Aschoff lesions in similar material reported by Sabiston and Follis[8] is considerably higher, 32 of 43 specimens.

The high incidence of Aschoff lesions in the present study, 45.3 per cent of 183 auricular specimens, does not differ greatly from the incidence of Aschoff bodies noted in various series of autopsied cases of rheumatic heart disease. Rothschild, Kugel and Gross[15] report the finding of Aschoff bodies in 95 of 161 autopsied cases of rheumatic heart disease. Other evidences of rheumatic activity, such as pericarditis, acute myocarditis and auriculitis, were found in an additional 11 of their cases. The high incidence of activity reported by these authors was in material which had been examined by the standardized method of Gross, Antopol and Sacks[16] by which no less than six sections, representative of the most likely sites for rheumatic activity, are examined. Wartman and Hellerstein[17] noted activity in 34 of 120 cases. Claiborne and Wolff[18] collected 62 cases of rheumatic heart disease from autopsy records and found Aschoff bodies in 22 of them. The frequency with which Aschoff lesions are found in the heart depends upon the amount of cardiac tissue examined and also upon the age composition of the group being studied, a higher incidence occurring in younger persons.[15] This relationship of rheumatic activity to age also obtains in the present study as is pointed out elsewhere.[14]

TABLE 1.—*Aschoff Bodies in Auricular Appendages*

	Boston City Hospital		Peter Bent Brigham Hospital		Total	
No. of appendages	44		179		223	
No. rejected	3		37		40	
Quantity insufficient	1		6		7	
Doubtful lesions	2		8		10	
Other	0		23		23	
No. studied	41		142		183	
Aschoff bodies present	18	43.8%	65	45.8%	83	45.4%
1 plus	3	7.3	25	17.6	28	15.3
2 plus	6	14.6	28	19.7	34	18.6
3 plus	9	21.9	12	8.5	21	11.5
Total 2 and 3 plus	15	36.5	39	28.2	54	30.1

AURICULAR THROMBOSIS

One hundred seventy-two auricular appendages have been studied for the presence of fresh or organized endocardial thrombi, 41 from the Boston City Hospital and 131 from the Peter Bent Brigham Hospital. Fresh thrombi were infrequent and presented as small laminated masses of fibrin containing entrapped erythrocytes and leukocytes, the latter often showing nuclear disintegration. More frequent were organized thrombi which were identified by the presence of vascularized tufts of fibrous tissue usually showing hemosiderin pigmentation. Adjacent to many of these areas of organization, particularly the more cellular ones, could be found focal collections of lymphocytes and plasma cells. These were not regarded as evidence of rheumatic activity, but rather as a nonspecific inflammatory infiltrate accompany-

ing the reparative process. Seventy-one of the 172 specimens studied showed evidence of fresh or organized endocardial thrombosis (table 2), an incidence of 41.3 per cent. Only seven of the specimens showing auricular thrombosis also presented Aschoff lesions, an incidence of 4.1 per cent, which is significantly lower than the over-all incidence of Aschoff lesions in the entire series.

The finding of a decreased incidence of rheumatic activity in the presence of auricular thrombosis has previously been reported. Weiss and Davis[19] found auricular thrombosis in 28 of 164 cases of rheumatic heart disease in which the disease was directly responsible for death. Among the 28 cases showing auricular thrombosis, rheumatic activity was noted in five and suggested in another. The activity in the cases showing thrombosis was 18 per cent as contrasted with an over-all incidence of activity of 47 per cent in the entire series. Weiss and Davis also point out that auricular fibrillation had been present in 22 of 25 cases showing thrombosis in which the rhythm was known. Biörck, Winblad and Wulff[7] point out, in connection with their study of auricular appendages, that Aschoff bodies were infrequent in the specimens showing thrombosis. Söderström[20] also, in studying auricular mural thrombosis, noted that rheumatic granulomas are rare in cases with auricular thrombosis. Graef, Berger, Bunim and de la Chapelle[21] studied 24 cases of rheumatic heart disease showing auricular thrombosis and noted a history of auricular fibrillation in 14 of these and other arrhythmias in two other cases. Microscopic findings interpreted as indicative of rheumatic activity were noted in 14 of their 24 cases, a much higher incidence than that noted in the present study or in that of Weiss and Davis. The specific lesions noted were a superficial auricular endocarditis in one case and collections of lymphocytes, histiocytes and basophilic mononuclear cells with occasional swelling of collagen fibers in the other cases. No Aschoff bodies were seen. The frequent occurrences of nonspecific inflammatory changes in areas involved by endocardial thrombosis makes these findings difficult to interpret. De la Chapelle, Graef and Rottino[22] studied 92 rheumatic hearts in detail according to the method of Gross, Antopol and Sacks[16] and came to the conclusion that auricular thrombosis in rheumatic heart disease was encountered most frequently in the hearts of individuals with auricular fibrillation, severe mitral stenosis and active rheumatic inflammation. The differences between these observations and those of Biörck, Winblad and Wulff,[7] Weiss and Davis,[19] Söderström[20] and of the present study are possibly related to the nature of the material studied and the number of sections taken. In a study of auricular thrombosis in hearts showing mitral stenosis, McGoon and Henly[23] found little difference in the activity of rheumatic lesions in the hearts, as determined by microscopic study, whether associated with auricular thrombosis or not. In studying auricular appendages removed at the time of surgical intervention for the correction of mitral stenosis, Sabiston and Follis[8] noted the presence of auricular thrombosis in 13 of 43 auricular specimens. Nine of the specimens showing thrombosis also showed Aschoff lesions.

TABLE 2.—*Incidence of Thrombosis in Auricular Appendages*

	Boston City Hospital	Peter Bent Brigham Hospital	Total
No. of appendages	41	131	172
Thrombosis present	14 34.1%	57 43.5%	71 41.3%
Thrombosis with Aschoff bodies	1 7.1%	6 4.6%	7 4.1%

The only common factor associated with auricular thrombosis by various authors[19-21, 23-28] is the presence of auricular fibrillation in the majority of cases, and it is generally agreed that there are no characteristic histologic changes associated with this state.[4, 25, 29] The present series is studied with reference to the presence of auricular fibrillation elsewhere.[14]

AUTOPSIED CASES

Autopsies were performed on 21 patients whose auricular appendages are included in this series. An additional patient is included

who died after the termination of the auricular biopsy series. Eight of the autopsies were performed at the Boston City Hospital and 14 at the Peter Bent Brigham Hospital. The number of autopsies at the former hospital is swelled by the presence of five cases from 1950 when the surgical technic for the correction of mitral stenosis was not well developed and the criteria for operability not well defined. Survival time after operation was 11 days or less in 21 of the 22 cases. One patient came to autopsy 16 months after operation. Aschoff lesions were present, either in the auricular appendage or in the remainder of the heart at autopsy, in 6 of these 22 autopsied patients (table 3). Five patients among the 22 showed Aschoff lesions in the auricular appendage, and five also showed Aschoff lesions in the remainder of the heart at autopsy. It may be noted, however,

TABLE 3.—*Autopsied Patients Showing Aschoff Lesions*

Case	Sex	Age	Auricular Lesions	Ventricular Lesions	Survival
1	F	46	+++	+	6 days
2	F	34	+	0	7 days
3	F	28	++	+	12 hours
4	F	45	++	+++	16 months
5	M	48	0	+	2 hours
6	M	42	+	+	7 days

that the two groups do not coincide. Patient 2 showed minimal evidence of rheumatic activity in the auricular appendage (fig. 1) but failed to show recognizable activity in the remainder of the heart at autopsy seven days after operation. Patient 5 showed minimal activity in the left ventricular myocardium at autopsy, whereas no recognizable Aschoff body had been present in the original specimen of the auricular appendage. The three patients who evidenced activity graded 2 plus and 3 plus in the appendages did not fail to show Aschoff lesions in the heart at autopsy (figs. 5 and 6). Patient 4, whose auricular appendage was graded as showing activity of 2 plus degree, showed at autopsy 16 months later the most extensive rheumatic carditis noted in any case studied. Aschoff bodies were noted in 7 of 20 sections prepared from the heart. The lesions were chiefly in the left ventricular myocardium, as is true of the other cases showing active lesions at autopsy as well, but occasional lesions were also noted in this case in the left auricular endocardium and in the root of the pulmonary valve. No valvular endocarditis of acute type was noted in any of the hearts studied at autopsy.

Although the number of cases is small, these findings suggest that frequent Aschoff bodies in the auricular appendage are paralleled by the presence of Aschoff bodies throughout the remainder of the heart, particularly the left ventricular myocardium. Nowhere do they appear in such profusion, however, as in the appendages showing the highest degree of activity (fig. 2). Occasional Aschoff bodies, representing minimal activity, may be found either in the appendage or in the remainder of the heart unassociated with detectable activity elsewhere. It is for this reason that it is felt that activity of the degree graded 2 plus and 3 plus may have a somewhat greater significance than the occasional minimal lesions graded 1 plus.

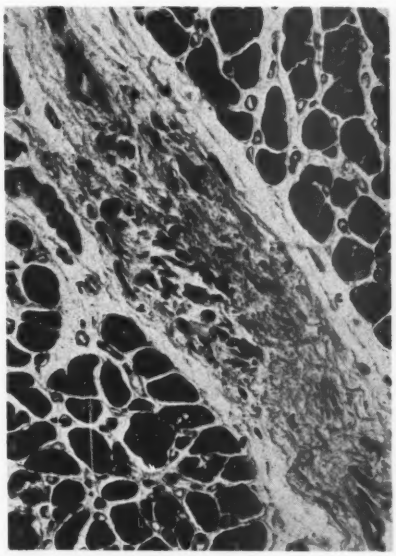

FIG. 6. Aschoff body from left ventricular myocardium of autopsied case 1.

Because of the paucity of information concerning the pathologic anatomy of the auricular appendage in rheumatic heart disease and its relationship to rheumatic activity elsewhere in the heart, 11 hearts presenting unequivocal

stigmata of rheumatic disease were selected from the autopsy material at the Boston City Hospital. Each of these hearts was studied according to the standardized method of Gross, Antopol and Sacks.[16] Additional sections were taken from the left auricular appendage. Two hearts of the 11 showed rheumatic activity. One of these was from a man of 82 who died with congestive heart failure following myocardial infarction. Rare Aschoff lesions were found in both the auricular appendage and in the left ventricular myocardium. The other active case was that of a 37 year old man with aortic stenosis in whose heart numerous Aschoff bodies were seen in the auricular appendage and in the left ventricular myocardium. The findings in this series of 11 cases of rheumatic heart disease are thus in general agreement with those in the larger series of autopsied patients who died following corrective surgery on a stenotic mitral valve.

Conclusions

1. A study of 183 left auricular appendages, removed at the time of surgical correction of mitral stenosis, shows evidence of active rheumatic carditis as determined by the presence of Aschoff bodies in 83 (45.3 per cent). This incidence is in general agreement with that reported in various series of autopsied cases of rheumatic heart disease.

2. Old or recent auricular thrombosis was noted in 71 of 172 auricular appendages (41.3 per cent). This group shows a decreased incidence of Aschoff lesions (4.1 per cent) when compared with the entire group (45.6 per cent).

3. In 6 of 22 cases in which autopsy was done rheumatic activity was noted in either the auricular appendage or the remainder of the heart. In the cases in which Aschoff bodies were frequent in the appendage, they were also present in the remainder of the heart, chiefly the left ventricular muscle. Minimal auricular and ventricular lesions were unassociated in two cases, suggesting that the correlation of activity in the two locations is poor at minimal levels.

Summary

Auricular appendages from patients undergoing operation for mitral stenosis have been studied with regard to presence of Aschoff bodies and endocardial thrombosis and correlated with Aschoff bodies in the remainder of the heart. Aschoff bodies were found in 45 per cent of 183 appendages, endocardial thrombosis in 41 per cent. Aschoff lesions and thrombosis occurred together in only 4 per cent. In cases in which Aschoff bodies were frequent in the appendage, they were also found in the remainder of the heart in autopsied patients.

Sumario Español

Las apéndices auriculares izquierdas de 183 pacientes removidas durante la operación para estenosis mitral fueron estudiadas con referencia a la presencia de cuerpos de Aschoff y trombos endocardiales. Una incidencia general de cuerpos de Aschoff de 40 por ciento se encontró. Un significante decremento en lesiones de Aschoff en la presencia de trombosis se encontró. El hallazgo de cuerpos de Aschoff en las apéndices se correlaciona con los hallazgos en el restante del corazón en casos sometidos a autopsia.

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Hypertension and Coronary Occlusion

By ARTHUR M. MASTER, M.D.

The problem of the relationship between hypertension and coronary occlusion has been re-examined. Using newly established limits of hypertension, 600 consecutive private patients with coronary occlusion—500 men and 100 women—all under 65 years of age, were studied. Hypertension did not appear to be a factor in producing coronary disease and occlusion among men, but was a definite factor in its causation among women. The possible relation of the serum cholesterol, the S_f 12–20 lipoprotein fraction, and the sex hormones to atherosclerosis and hypertension is discussed.

EVER since coronary occlusion became a well recognized clinical entity, many writers have suggested that hypertension was a common antecedent of the condition in both men and women, and a significant factor in its etiology.[1-25] My colleagues and I, also, have reported similar findings,[10, 14, 19] and have concurred in these opinions.

Thus, in 1939, Master, Dack, and Jaffe[14] studied 500 patients with coronary artery occlusion, 387 men and 113 women. Using a systolic pressure of 150 mm. Hg and/or a diastolic pressure of 90 mm. Hg as a definition of hypertension, they found that 219 of the men (56.5 per cent) and 90 of the women (80 per cent) were hypertensive; an average of 61.8 per cent. The number of patients who had had hypertension prior to the coronary occlusion was found to increase with advancing age. Thus, only 28 per cent of the men below 35 years of age were hypertensive, but the incidence rose rapidly to 80 per cent, at and above the age of 70 years. In the women with coronary occlusion, hypertension was found to be even more common than in the men, and to increase in frequency more rapidly; it was present in only 25 per cent of those below 35 years and in from 90 to 100 per cent of those who were 45 years of age or over.

In 1943, in a similar study, Master, Jaffe, Dack and Silver,[19] employing a systolic blood pressure of 150 mm. Hg and/or a diastolic pressure of 96 mm. Hg as evidence of hypertension, found that 69 per cent of all the patients had suffered from hypertension before the coronary artery occlusion had occurred.

From the foregoing reports, it appeared that hypertension was an important predisposing factor in coronary occlusion, particularly in the older age groups and especially in women. Apparent confirmation of this opinion was found in the greater incidence of "hypertension" in patients with coronary occlusion than in the general population.[10, 19, 26] Thus, for example, in the study to which reference was just made, "hypertension" was found to be four or five times more frequent in the 25 to 54 year age group of males and females with coronary occlusion, and two to three times more frequent in the 55 to 74 year group, than it was among the general population.

However, even in 1939, Master, Jaffe and Dack[14] emphasized the fact that hypertension was not the only etiologic factor in coronary occlusion, since the majority of patients under 45 was not hypertensive. Durant[27] and also Franklin[28] questioned the relationship between hypertension and coronary occlusion. In retrospect, it seems obvious that the premise that "hypertension" caused coronary occlusion was untenable, since one definition of hypertension was applied to all ages and to both sexes. Furthermore, in the cited report of Master, Jaffe and Dack[14] the prognosis was found to be the same, whether hypertension was or was not present. Conner and Holt,[5] as well as many others,[4, 14, 16, 21-23, 29-32] had also found that the occurrence of hypertension was of no significance in the prognosis of coronary thrombosis.

It is now our opinion that the conclusions formerly reached concerning the relationship of hypertension to coronary occlusion are not valid. "High" systolic and diastolic blood pres-

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Read in part before the Interim Meeting of the American Medical Association, Cleveland, Ohio, December 7, 1950.

sures have been found in the majority of all persons 60 years of age and older. Readings previously believed to be abnormal are too common to be considered so now.[33] New definitions of hypertension, according to the age and sex of the patients, were evidently necessary. Since the average blood pressure rises with age and varies with sex, it is not reasonable to use the same definition of hypertension, for example, 150/90, or 150/96, or 160/100, for all ages, and for both men and women.

In order to obtain more accurate and more correct limits of hypertension, varying for different age groups, and for both sexes, Master, Dublin, and Marks[34, 35] adequately sampled and statistically analyzed the blood pressure readings of 74,000 working men and women between the ages of 16 and 65 years. The normal blood pressure range found in these studies and the proper limits of hypertension thus established are more liberal than those usually employed; they are, however, conservative, when compared with the findings of others, who studied the blood pressure measurements in comparable groups of individuals.[34]

Using these recently established limits of hypertension as the basis for our new study, we re-examined the problem of the relationship between hypertension and coronary occlusion. Six hundred consecutive patients with coronary occlusion, seen in private practice, were studied. Five hundred were men and 100 were women, all under the age of 65. Patients over 64 were not included in this study, solely because the newly established blood pressure limits had not been determined for individuals beyond that age. To this extent, therefore, the group studied was a selective one. This relative selectivity was not significant, however, since only 6 per cent of the male population of New York City and less than 7 per cent of the female population were more than 64 years old, during the time of this study (1946-1947-1948).[36]

TABLE 1.—*Normal Range and Limits of Systolic Hypertension**

Age	Normal Range		Hypertension Lower Limit	
	Male	Female	Male	Female
16	105–135	100–130	145	140
17	105–135	100–130	145	140
18	105–135	100–130	145	140
19	105–140	100–130	150	140
20–24	105–140	100–130	150	140
25–29	108–140	102–130	150	140
30–34	110–145	102–135	155	145
35–39	110–145	105–140	160	150
40–44	110–150	105–150	165	165
45–49	110–155	105–155	170	175
50–54	115–160	110–165	175	180
55–59	115–165	110–170	180	185
60–64	115–170	115–175	190	190

* From the Bulletin of the New York Academy of Medicine, **27**: 452, 1951.

TABLE 2.—*Normal Range and Limits of Diastolic Hypertension**

Age	Normal Range		Hypertension Lower Limit	
	Male	Female	Male	Female
16	60–86	60–85	90	90
17	60–86	60–85	90	90
18	60–86	60–85	90	90
19	60–88	60–85	95	90
20–24	62–88	60–85	95	90
25–29	65–90	60–86	96	92
30–34	68–92	60–88	98	95
35–39	68–92	65–90	100	98
40–44	70–94	65–92	100	100
45–49	70–96	65–96	104	105
50–54	70–98	70–100	106	108
55–59	70–98	70–100	108	108
60–64	70–100	70–100	110	110

* From the Bulletin of the New York Academy of Medicine, **27**: 452, 1951.

It is evident that the blood pressure which had been present *before* the coronary occlusion occurred is the criterion, since the arterial tension almost invariably falls after the coronary occlusion. The preocclusion pressure was, therefore, definitely ascertained in 478 of our 600 patients. In many of the 478 cases, the writer had himself recorded the blood pressure before the occlusion occurred. In the others the information was obtained directly from the referring physician, or from the patients, if they actually knew their previous blood pressure readings. In the remaining 122 patients, clinical judgment was used in estimating the previous blood pres-

sure. Cognizance was taken of the fact that the blood pressure usually falls rapidly and early in the attack of coronary occlusion, and that about one-third of the hypertensive patients thereafter permanently loses their hypertension.[19] Hence, if, for example, on the second or third day of the coronary occlusion, the blood pressure was 160/100 mm. Hg, it was concluded that the pressure had probably been higher before the attack. If it was 180 to 240 mm. Hg systolic and 120 to 140 mm. Hg diastolic during the first and second days (a tension found in a recent case of coronary occlusion), hypertension was believed to have been present previously, in spite of the fact that the blood pressure prior to the attack was unknown, and in spite of the further fact that the blood pressure had continued to be normal—110 to 130 systolic and 80 to 90 mm. diastolic—for from 1 week to 14 months after the occlusion. If the blood pressure returned to a hypertensive level after a few months, or within a year after the attack of coronary occlusion, it was assumed that the patient had had hypertension before the attack. Finally, typical eyeground changes, an enlarged heart with characteristic contour of the left ventricle and aorta, and a typical electrocardiographic pattern of left ventricular strain were considered to be acceptable evidences of the presence of hypertension.

A few of the patients had "borderline" blood pressures, that is, blood pressure readings higher than the normal range, but not quite elevated to the limit definitely demarcating "hypertension."[34] The borderline cases were not considered in this report, because they were so few, and because a clearer impression can be obtained by comparing patients who had definitely elevated blood pressure with those who had definitely normal blood pressure.

Of the 500 male patients who suffered a coronary occlusion (table 3) the largest number (25.6 per cent) was between 50 and 54 years of age; 23.0 per cent were between 55 and 59 years of age, 17.9 per cent were 45 to 49 years old, 15.4 per cent were 40 to 44 years old, 12.6 per cent were 60 to 64 years old. Thus, almost half of the male patients were between 50 and 60 years of age. These seem to be the dangerous years for coronary occlusion, at least when men under 65 are considered. Nevertheless, nearly two-fifths (38.7 per cent) of the patients were under 50 years of age.

The frequency of hypertension among the 500 male patients averaged 27.2 per cent. Beginning with the age of 40, when the number of cases was large enough to be statistically significant, the increase in the frequency of hypertension with age was barely perceptible. In the 40 to 49 year age group, the frequency of hypertension was 26 per cent; in the 55 to 59 year age group, it was nearly 29 per cent; and in the 60 to 64 year age group, it was 30 per cent. Thus, the frequency of hypertension, among men with coronary occlusion, increased only slightly, if at all, with the increasing years.

TABLE 3.—*Blood Pressure in Coronary Occlusion. 500 Males*

	Total		Hypertension		Borderline		Normal	
	No.	% of Total	No.	%	No.	%	No.	%
All ages (25–64)	500	100.0	136	27.2	32	6.4	332	66.4
25–39	27	5.4	6	22.2	1	*	20	74.1
40–44	77	15.4	20	26.0	3	3.9	54	70.1
45–49	90	17.9	23	25.6	5	5.6	62	68.8
50–54	128	25.6	35	27.3	6	4.7	87	68.0
55–59	115	23.0	33	28.7	10	8.7	72	62.6
60–64	63	12.6	19	30.4	7	11.0	37	58.6

* Less than 3 cases, per cent not calculated.

Only 27 per cent of the 500 men had had hypertension before the coronary occlusion occurred, whereas more than 70 per cent had had normal blood pressures previously. It would certainly appear, therefore, that hypertension, if it is a factor at all, is not the all important one in *men* who sustain coronary occlusion. This conclusion is at variance with that of any other reported study on the relationship of the blood pressure to the onset of coronary occlusion.

To determine the relation of hypertension to coronary occlusion in *women*, we studied the histories of 100 women, examined consecutively, with coronary occlusion (table 4). Among the 100 women, coronary occlusion occurred at a later age than among the men. The largest number (32 per cent) of the female

patients was between 60 and 64 years of age; 28 per cent were between 55 and 59 years of age; 18 per cent were between 50 and 54 years of age. Thus, three-fifths of the female patients were 55 years of age or older, whereas barely 22 per cent were less than 50 years old.

A tabulation of the blood pressure incidence of hypertension in the 100 women who sustained coronary occlusion is shown in table 4. Seventy-one per cent of the women had had hypertension preceding the attack, according to the new limits established by Master, Dublin and Marks.[34] The actual number of female patients in each decade is too small, so that no conclusion can be drawn concerning the increasing incidence of hypertension with increasing age among women. We can say definitely, however, that hypertension *was a very significant factor in women* who sustained coronary occlusion. This is quite different from the conclusion drawn from the observations among the men.

TABLE 4.—*Blood Pressure in Coronary Occlusion. 100 Females*

	Total		Hypertension		Borderline		Normal	
	No.	% of Total	No.	% of Total	No.	% of Total	No.	% of Total
All ages (35–64)	100	100.0	71	71.0	8	8.0	21	21.0
35–49	22	22.0	14	63.7	2	*	6	27.3
50–54	18	18.0	14	77.8	0	0	4	22.2
55–59	28	28.0	18	64.4	3	10.6	7	25.0
60–64	32	32.0	25	78.2	3	9.3	4	12.5

* Less than 3 cases, per cent not calculated.

Even when the newer, more liberal definition of hypertension is employed, hypertension is, apparently, just as common among women as it was when the much lower limits of high blood pressure were accepted as criteria. The probable explanation for this seeming contradiction lies in the fact that women over the age of 55 more often suffer from coronary occlusion; in this age group, relatively "high" blood pressures are as frequent, whether the new definitions of hypertension, or whether the old limits (150 mm. Hg systolic and/or 90 mm. Hg diastolic) are used.

The results of a recent postmortem study by Zeman and Schwartz[37] are in keeping with the findings reported in this clinical study, namely, that hypertension does not appear to be a factor in producing coronary disease and occlusion among men, but is a definite factor in its production among women. Zeman and Schwartz[37] reported on a postmortem study of 154 unselected patients, from the Home for Aged and Infirm Hebrews of New York City. All had been over 60 years of age; 66 were males and 88 were females. The subjects were divided into three groups: those who had had a normal blood pressure, those who had had a systolic hypertension, and those who had had both a systolic and a diastolic hypertension. Among the males, in these three groups, no significant difference was found in the incidence of coronary occlusion. About one-third of all the males had had a coronary occlusion. None of the females, who had had a normal blood pressure, suffered from a coronary occlusion; those who did suffer from an occlusion had either a systolic hypertension or both a systolic and a diastolic hypertension.

Discussion

The average age of the men who sustained a coronary occlusion (51.1 years) was lower than that of the women (54.8 years), a difference of almost 4 years. In another recently reported series the difference was even greater, that is, the women were 6.4 years older at the time of the attack.[38]

Men developed coronary occlusion much more frequently than did women; furthermore, it occurred at an earlier age in men, and only one-fourth of the men had had hypertension prior to the attack. On the other hand, the majority of women who sustained a coronary occlusion did have hypertension, and they were, on the average, four or five years older than the men. What accounts for these differences between the sexes, and how significant are they? The following brief explanations seem plausible, but it should be remembered that they are theoretic, and are based merely on some suggestive data.[39]

The normal serum cholesterol, the Gofman lipoprotein fraction S_f 12–20, and the beta-lipoprotein fraction of the blood have been found to vary with sex and age.[40-45] In men,

the serum cholesterol reaches its peak at the age of 55, and in women between the sixtieth and seventieth years. This may account, in part, for the later occurrence of coronary occlusion in women. In men, the Svedberg flotation fraction of the blood, that is, the S_f 12–20 lipoproteins, rises from 25 mg. per 100 cc. at the age of 25 to 39 mg. per 100 cc. at the age of 30, and remains at that high level until the sixtieth year. In women, on the contrary, the rise is slow between the age of 25 and 60. Only at the age of 60, do women attain the high figure which men have at the age of 30. This, too, may account for the greater incidence and earlier occurrence of coronary artery disease and coronary occlusion in males. In men, between the ages of 18 and 35, there is more beta-lipoprotein in the plasma than in women of the same age. This is another possible cause for the earlier development of coronary sclerosis in males. Dock's[46] finding that the intima of the coronary arteries in the newborn male is thicker than in the newborn female may also account for the greater frequency of coronary disease in men.

We have shown that three-fourths of the women with coronary occlusion and only one-quarter of the men had had previous hypertension, according to the new criteria. The serum cholesterol and the S_f 12–20 lipoprotein ratio are higher in patients with hypertension than in those with normal blood pressure,[42, 47, 48, 49] and may be the factors through which hypertension accelerates atherosclerosis. Why hypertension is a prerequisite for the development of coronary disease and occlusion among the majority of women, and only among a minority of men, is not clear.

The normal arterial tension is slightly higher in women than in men, beginning at the age of 45 to 50. Whether this is sufficient to initiate or accelerate the process of atherosclerosis in women, at the age of 55 to 60, is questionable. Our study of 74,000 gainfully employed people[34] indicates that, until the age of 45, women have a definitely lower blood pressure than men, but that thereafter their pressure is slightly higher than that found in men. The difference is small but distinct. If one agrees with Moschowitz,[50] who believes that heightened arterial tension eventually produces arteriosclerosis, this difference in normal blood pressure in the sexes may serve as a possible explanation of the earlier occurrence of coronary disease and occlusion among men than among women.

The continued investigation of the blood lipoproteins seems to be a promising avenue of approach to the problem of coronary disease. The discovery of means to keep this blood fraction low may help to prevent coronary disease, and lead even to the prevention of hypertension.

For many years, the relationship of both arteriosclerosis and hypertension to the sex hormones has been a subject of intriguing speculation. The predominance of coronary artery atherosclerosis in men[14] has suggested that female sex factors protect women. Many investigators[51-55] have described the beneficial effect of androgens and estrogens in angina pectoris among men and in hypertension among women. A review of the literature on this subject may be found in Hueper's monograph on "Arteriosclerosis."[56] However, estrogens have usually been found to be ineffective clinically in coronary disease of men. Furthermore, the observations that the estrogens reduce the serum lipids in those with coronary atherosclerosis have not gone unchallenged. Glass, Engelberg, Marcus, and Gofman[57] have administered estrogens in men and women but found no significant change in the cholesterol-lipid ratio or in the S_f 12–20 lipoprotein fraction. Altogether, the field of sex hormonal treatment has not been investigated adequately.

Summary and Conclusion

Hitherto, hypertension was believed to be a common antecedent of coronary occlusion in both men and women, and a significant factor in its etiology. This belief was invalid, since the same definition of hypertension was employed in patients of all ages and in both sexes.

New definitions of hypertension, varying with the age and sex of the patients, were, therefore, necessary. These were established by Master, Dublin and Marks, who adequately sampled and statistically analyzed the blood pressure readings of 74,000 working men and women, between the ages of 16 and 65.

The problem of the relationship between hypertension and coronary occlusion was then re-examined. Using these newly established limits of hypertension, we studied 600 consecutive private patients with coronary occlusion—500 men and 100 women—all under the age of 65 years.

The blood pressure which had been present before the coronary occlusion occurred was the criterion. (The borderline cases were not considered in this report.)

Men sustain coronary occlusion much more frequently than women, and at an earlier age.

The frequency of hypertension in the men averaged 27.2 per cent, and increased only slightly, if at all, with age. More than 70 per cent had had a normal blood pressure before the onset of the coronary occlusion! Hypertension, therefore, is not the all important factor in the causation of coronary occlusion in men. This conclusion differs from that of any reported studies on the relationship of increased blood pressure to the onset of coronary occlusion.

Seventy-one per cent of the women had had hypertension preceding the attack. In women who sustain coronary occlusion, therefore, hypertension is a very significant etiologic factor.

The results of a recent postmortem study confirmed our clinical findings: hypertension did not appear to be a factor in producing coronary disease and occlusion among men, but was a definite factor in its causation among women.

The possible effects of the serum cholesterol, the S_f 12–20 lipoprotein fraction, and the sex hormones on atherosclerosis and hypertension have been briefly discussed. These fields of investigation hold particular promise for the treatment and prevention of coronary disease in men and of hypertension in women.

Sumario Español

El problema de la relación entre la hipertensión y la oclusión coronaria ha sido reexaminado. Usando los nuevos establecidos límites para la hipertensión, se estudiaron 600 casos privados consecutivos (500 hombres y 100 mujeres) todos bajo la edad de 65 años. La hipertensión no aparentó ser un factor en la producción de enfermedad coronaria u oclusión en los hombres, pero si fué un factor definitivo en las mujeres. La posible relación del colesterol del suero, la fracción de lipoproteinas S_f 12–20, y las hormonas sexuales a la ateroesclerosis y la hipertensión se discute.

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Pulmonary Function in Rheumatic Heart Disease and Its Relation to Exertional Dyspnea in Ambulatory Patients

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Pulmonary and cardiocirculatory function were studied in 21 ambulatory patients with rheumatic heart disease. A pattern of pulmonary function was observed which deviated from normal to a degree insufficient to account for the exertional dyspnea of these patients. The pathogenesis of this symptom is, therefore, discussed in relation to the observed cardiocirculatory abnormalities which were often pronounced.

WITH few exceptions, notably the reports by Peabody and co-workers[1, 2] on maximal pulmonary ventilation induced by rebreathing expired air, studies directed at the problem of dyspnea of cardiac origin have been limited to determinations of pulmonary ventilation at rest and during exercise as well as measurement of various lung volumes in patients with heart disease.[3-11] While the presence of functional impairment of the lungs has been deduced from various abnormalities noted in these tests[2, 3, 4, 5, 7] particular emphasis has been placed upon the value of the vital capacity determination. According to one viewpoint the importance of this measurement lies in the beliefs, first, that dyspnea in heart disease is simply a manifestation of insufficiency of the pulmonary ventilatory apparatus due to both an increased ventilatory requirement and a decreased ventilatory capacity[1, 2, 3, 4, 7] and, second, that the vital capacity affords a reliable index of this ventilatory capacity.[2, 3, 6, 7, 8] According to another opinion, however, one which stresses the point that cardiac dyspnea is largely "reflex" in nature,[12] the vital capacity is important chiefly because it is a good index of pulmonary elasticity, a decrease in which is considered to be the main factor in the origin of "reflex" dyspnea. All of these concepts are, however, open to some doubt[13, 14] and are deserving of re-examination. Vital capacity has not proved to be a reliable index of ventilatory capacity in many forms of chronic pulmonary disease[15, 16, 17] and may not be so in the case of heart disease. A causal relationship, furthermore, between the symptom of dyspnea in cardiac patients and the postulated insufficiency of the ventilatory apparatus, while plausible, has not been demonstrated.

Studies emphasizing dynamic concepts of pulmonary function as well as lung volume measurements have proved to be more useful than the latter alone in defining patterns of pulmonary dysfunction in chronic pulmonary disease[16, 17] and might be expected, therefore, to provide a means of evaluating the performance of the lungs in heart disease. The present report deals with a series of such pulmonary function studies as well as various cardiocirculatory measurements in a group of patients with rheumatic heart disease who presented varying degrees of exertional dyspnea.

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This work was supported, in part, by grants from the New York Heart Association and the Charles A. Frueauff Research Gift.

This work was done, in part, during Dr. West's tenure of a Life Insurance Medical Research Fellowship and while Dr. Bliss was a Post-doctorate Fellow, United States Public Health Service.

METHODS OF STUDY

The pulmonary function of 21 individuals suffering from chronic, inactive rheumatic heart disease was studied according to methods previously described[13] (table 1). Eighteen of these patients, group I, with uncomplicated heart disease, were free from edema, ascites, obvious hepatomegaly and pulmo-

TABLE 1.—*Clinical Findings in 21 Patients with Rheumatic Heart Disease, Inactive, at the Time of the Physiologic Studies*

Patient	Sex	Age	B.S.A.	Remarks
				Group I
A. D.	F	23	1.56	N.S.R., M.S. No exertional dyspnea. No digitalis. Never in cardiac failure.* Class I. A
J. S.	M	42	1.72	N.S.R., M.S. Dyspnea only on strenuous exertion. No digitalis. Never in cardiac failure. Class I. A
J. R.	M	48	1.74	N.S.R., M.S. Dyspnea on moderate exertion. No digitalis. Never in cardiac failure. Class II. C
M. R.	F	32	1.45	N.S.R., M.S. Dyspnea on mild exertion. Digitalized. Previous cardiac failure. Class II. C
M. D.	F	34	1.61	N.S.R., M.S., E.H. Dyspnea on moderate exertion. Digitalized. Never in cardiac failure. Class III. D
H. R.	F	36	1.64	N.S.R., M.S., M.I., E.H. Dyspnea on mild exertion. Digitalized. Previous cardiac failure. Class III. C
G. K.	F	24	1.81	N.S.R., M.S., M.I. No exertional dyspnea. No digitalis. Never in cardiac failure. Class I. A
N. W.	M	18	1.70	N.S.R., M.S., M.I., E.H. Dyspnea on moderate exertion. No digitalis. Never in cardiac failure. Class II. C
E. S.	M	36	1.89	N.S.R., M.S., M.I., E.H. Dyspnea on moderate to severe exertion. Digitalized. Previous cardiac failure. Class II. C
E. C.	M	24	1.70	N.S.R., M.S., M.I., E.H. Dyspnea on moderate to severe exertion. No digitalis. Never in cardiac failure. Class II. C
H. C.	F	44	1.65	N.S.R., M.S., M.I., E.H. Dyspnea on mild exertion. Digitalized. Previous cardiac failure. Class III. C
V. H.	F	30	1.41	Aur. Fib., M.S., M.I., E.H. Dyspnea on mild exertion. Digitalized. Never in cardiac failure. Class III. C
A. A.	F	37	1.40	Aur. Fib., M.S., M.I., E.H. Dyspnea on mild exertion. Digitalized. Previous cardiac failure. Class III. C
L. A.	F	25	1.65	Aur. Fib., M.S., M.I., E.H. Dyspnea on mild exertion. Digitalized. Previous cardiac failure. Class III. C
R. D.	F	42	1.57	Aur. Fib., M.S., M.I., E.H. Dyspnea on least exertion. Digitalized. Previous cardiac failure. Prolonged bed rest. Class IV. D
A. B.	F	15	1.81	N.S.R., M.I., A.I. No exertional dyspnea. No digitalis. Never in cardiac failure. Class I. B
J. M.	M	17	1 75	N.S.R., M.S., M.I., A.I., E.H. No exertional dyspnea. No digitalis. Never in cardiac failure. Class I. B
G. M.	F	32	1.42	N.S.R., M.S., M.I., A.S., A.I., E.H. Dyspnea on slight exertion. Digitalized. Previous cardiac failure, recurrent pulmonary edema. Class III. D
				Group II
H. N.	M	33	1.76	Aur. Fib., M.S., M.I., E.H. Dyspnea on mild exertion. Digitalized. Previous cardiac failure. Class III. C. Chronic pulmonary emphysema.
H. H.	M	42	1.66	Aur. Fib., M.S., E.H. Dyspnea on least exertion. Digitalized. Previous cardiac failure. Class III or IV. D. Restrictive fibrosis secondary to pleural adhesions, right lung, following lung abscess, empyema and thoracotomy.
F. L.	F	37	1.64	Aur. Fib., M.S., M.I., E.H. Dyspnea on mild exertion. Digitalized. Previous cardiac failure. Class III. D. Bronchial asthma, chronic bronchitis, emphysema.

* The term "cardiac failure" as used here means right ventricular failure.

Abbreviations: B.S.A. = body surface area in square meters; N.S.R. = normal sinus rhythm; Aur. Fib. = auricular fibrillation; M.S. = mitral stenosis; M.I. = mitral insufficiency; A.S. = aortic stenosis; A.I. = aortic insufficiency; E.H. = enlarged heart.

nary rales at the time of study, although several gave a history of having had right ventricular failure or pulmonary edema or both at some time in the past. While a few of the patients were asymptomatic the majority complained of persistent exertional dyspnea which in some was quite severe. According to the criteria of the New York Heart Association[18] there were five in class I, five in class II, seven in class III and one in class IV. Three other patients, group II, presented definite clinical evidence of intrinsic pulmonary disease in addition to heart disease. They, too, were free from signs of congestive failure or pulmonary edema at the time of study, but each complained of severe exertional dyspnea. In all but four of the cases it was possible to measure cardiac output and right heart pressures by the cardiac catheterization technic shortly before or soon after the pulmonary function studies. Data on 10 additional patients, similar in every way to those in group I but studied only during cardiac catheterization, are also included in graphic form only for the purpose of illustrating the relationship of pulmonary ventilation to the cardiac index and mean pulmonary arterial pressure during a steady state of exercise

Cardiac catheterization was always performed in the morning hours with the patient in a postabsorptive state and, in general, without premedication. Venous cutdown, insertion of the catheter and simultaneous collection of samples of blood and expired air were performed in the usual manner for the determination of cardiac output by the direct Fick method. Expired air was measured in a Tissot gasometer and analyzed for oxygen and carbon dioxide in a Scholander micro gas analyzer.[19] Samples of mixed venous blood were withdrawn anaerobically from the right or left pulmonary artery just beyond the bifurcation, except in one instance (table 2) when right auricular blood was obtained. Arterial blood was obtained from an indwelling needle seated in a peripheral artery. The oxygen contents of both bloods were determined immediately after withdrawal by the manometric method of Van Slyke and Neill.[20] Intracardiac and intravascular pressures were recorded photographically via resistance wire pressure transducers and ballistic galvanometers.[21] Systolic and diastolic pressures reported here represent arithmetic mean values over at least two respiratory cycles and mean pressures were calculated over the same time period after planimetric integration of the areas beneath the curves.

Observations at rest were made while the patients were lying in a comfortable position on a fluoroscopic table. Exercise was performed in the same position, the patient moving weighted pedals with his feet. In an attempt to achieve as steady a metabolic state during exercise as was present at rest the patients were required to perform the exercise for 8 or 10 minutes as a rule, and collection of samples of blood and expired air for measurement of cardiac output was delayed until exercise had been underway for five minutes or more.* The pressure values for exercise which are reported were recorded just prior to or just after the cardiac output determination during exercise.

Results and Comments

Since it was possible in these studies to obtain more information about the heart and circulation than had been available in the majority of previous studies, an attempt has been made to correlate any deviations from normal in pulmonary function with abnormalities in cardiocirculatory dynamics. In many instances deviations from normal in the latter sphere were quite severe in that marked reductions in cardiac output and elevations in pulmonary arterial pressure were observed frequently (table 2).

1. Lung Volumes. There were no striking deviations from normal in the conventional lung volumes of the patients in group I. While the vital capacity in three patients (M. D., N. W. and L. A.) was found to be less than 85 per cent of that predicted, the average for the entire group was 99 per cent and the lowest value noted was 80 per cent. Residual volume and total lung capacity were also relatively unimpaired, the latter differing significantly from the predicted values in only 1 of the 18 patients (N. W., a poorly developed youth who had led a markedly restricted life since early childhood). The mean ratio of residual volume to total lung capacity in this group was 23 per cent and the maximum value observed was 34 per cent. In contrast, each of the three patients in group II had a significant reduction in vital capacity, an increase in residual volume, and an abnormally high ratio of residual volume to total lung capacity.

In view of some previous work on the lung volumes in heart disease[3, 5-11] the normal findings in this group of patients is noteworthy since it has become rather widely accepted that alterations in the vital capacity, residual volume and total lung capacity may result from engorgement of pulmonary blood vessels

* Three exceptions should be noted: in the case of patients H. C., A. A., and A. B. cardiac output was measured *during* the fifth minute of the exercise period.

whether or not there is associated edema of the lungs or of the abdominal viscera.[7, 22] The findings in these patients, who had no clinical evidence of fluid retention, would suggest that reported previously.[23] The finding, on spirography, in several instances of a slight degree of expiratory prolongation at the extreme expiratory position in the patients of group I

TABLE 2.—*Physiologic Findings Relative to Pulmonary and Cardiocirculatory Function in 21 Patients with Rheumatic Heart Disease, Inactive*

Patient	Data Obtained During Pulmonary Function Study											Data Obtained During Cardiac Catheterization					
	VC % of Pred.	TLC % of Pred.	RV/TC × 100	MBC % of Pred.	Oxygen Cons. cc/min./M.² BSA		Arterial Oxygen Saturation		Arterial pCO_2		Index of Intrapulmonary Mixing % N_2	Oxygen Cons. cc/min./M.² BSA		Cardiac Index L./min./M.² BSA		Pulmonary Arterial Pressure mm. Hg	
					Rest	Ex.‡	Rest	Rec.	Rest	Rec.		Rest	Ex.§	Rest	Exercise§	Rest s/d, m	Exercise s/d, m
Group I																	
A. D.	120	109	12	120	107	430	97	98	41	43	2.5	—	—	—	—	—	—
J. S.	110	104	19	77	123	383	94	97	45	45	1.1	129	300	2.87	4.16	20/ 6, 12	34/11, 20
J. R.	109	97	14	98	118	423	96	91	37	38	1.2	143	251	2.81	3.70	31/21, 24	52/29, 39
M. R.	90	98	27	95	110	476	95	98	38	37	1.0	123	—	2.61	—	47/21, 32	81/40, 53
M. D.	84	102	34	82	132	303	92	89	34	33	1.5	144	—	2.29	—	105/56, 74	128/67, 88
H. R.	90	—	—	93	143	317	93	98	31	22	—	149	367	2.12	2.48	69/30, 43	—
G K.	140	119	15	84	118	491	96	96	33	35	1.8	—	—	—	—	—	—
N. W.	80	75	15	82	140	427	98	97	45	47	2.4	—	—	—	—	—	—
E. S.	88	92	27	75	150	438	95	93	40	39	1.3	172	—	2.69	—	70/29, 42	—
E. C.	113	120	23	77	117	310	98	100	34	33	1.1	121	372	1.73	2.95	74/43, 55	117/67, 84
H. C.	91	94	26	82	107	347	100	95	—	32	2.1	118	186	2.37†	2.35†¶	48/24, 31	—
V. H.	94	104	27	90	121	289	98	95	37	35	1.2	140	207	2.08	2.52	32/16, 20	67/40, 43
A. A.	88	88	23	103	113	296*	97	—	33	—	1.2	110	269	1.44	1.89¶	24/14, 17	44/28, 37
L. A.	82	97	34	87	139	372	95	99	40	40	2.4	160	203	2.50	2.70	32/20, 25	50/29, 37
R. D.	103	109	27	60	143	288*	96	92	36	—	0.8	141	251	1.94	1.95	83/40, 54	121/69, 87
A. B.	108	108	14	81	120	517	98	—	36	—	2.6	142	294	4.17	5.16¶	19/ 7, 12	23/ 9, 16
J. M.	87	93	25	100	143	574	98	92	37	42	1.2	155	—	2.98	—	19/10, 14	—
G. M.	101	110	26	71	129	—	96	—	37	—	1.6	102	—	1.93	—	35/13, 23	—
Group II																	
H. N.	68	94	41	55	145	306*	88	89	42	42	2.3	143	246	2.34	2.80	39/18, 25	54/23, 36
H. H.	58	92	52	30	116	295*	94	95	36	36	2.6	133	203	1.68	1.88	91/51, 66	104/51, 68
F. L.	41	72	58	25	150	303*	94	95	42	40	2.5	—	—	—	—	—	—

* Patient performed slightly substandard exercise.

† Mixed venous blood sample withdrawn from right auricle.

‡ Thirty step test, duration: one minute.

§ Steady state exercise.

¶ Cardiac output determined during fifth minute of exercise.

Abbreviations: VC = vital capacity; TLC = total lung capacity; % of Pred. = per cent of predicted; RV/TC = residual volume/total lung capacity; Oxygen cons. = oxygen consumed; cc./min./M.² BSA = cubic centimeters per minute per square meter of body surface area; Ex. = exercise; Rec. = during the first minute of recovery after exercise; % N_2 = per cent of nitrogen in alveolar air after seven minutes breathing 100 per cent oxygen; L./min./M.² BSA = liters per minute per square meter of body surface area; s/d, m = systolic/diastolic, mean.

blood vessel engorgement alone, with or without cardiac enlargement, is not likely to result in a significant change in vital capacity or residual volume. These observations confirm similar findings in one other group of patients is perhaps pertinent to this matter. Observed in the absence of other stigmata of obstructive breathing, this may represent the early effect of a change in resilience of the lung (a decrease in compliance) secondary to engorgement of

the vascular bed, not sufficient to affect lung volume measurements in these patients but indicative of the effect more advanced circulatory abnormalities (pulmonary edema) might have.

2. Maximum Breathing Capacity. The maximum breathing capacities of 15 of the 18 patients in group I were less than the values predicted, but the average deviation from normal was small, the mean value for the group being 86 per cent of that predicted (table 2). The maximum breathing capacities of the three patients in group II were, in contrast, much lower than normal (table 2). There was no correlation in either group between maximum breathing capacity and resting cardiac index or mean pulmonary arterial pressure at rest. There was, also, no correlation between maximum breathing capacity and vital capacity in the patients in group I. The only instances of seriously reduced maximum breathing capacity among the patients in group I were noted in two cases (R. D. and G. M.) who were greatly debilitated as a result of prolonged hospitalization and bed rest. It would seem, therefore, that factors relating to general physical fitness are more important determinants of maximum breathing capacity in these patients with rheumatic heart disease than are specific circulatory changes. Recent work of another sort in this laboratory bears this out. Preliminary studies on a number of patients with mitral stenosis as well as normal individuals have shown that maximum breathing capacity determined *during* steady treadmill exercise is not different from that determined at rest. Were pulmonary vascular pressures, per se, an important determinant of maximum breathing capacity, physical exertion itself would tend to reduce this in most patients with mitral stenosis since an increase in pulmonary arterial pressure, with exercise, and undoubtedly pulmonary venous pressure as well, is the rule with this disorder.[24]

3. Spirograms. The findings with respect to lung volumes and maximum breathing capacity were, in general, reflected in the spirographic records. Normal spirograms were seen in the 18 cases of group I, except for the previously mentioned slight prolongation of expiration noted at the extreme expiratory position in a few instances. The three patients, on the other hand, whose clinical findings indicated intrinsic pulmonary disease were found to have spirograms that were quite abnormal: all demonstrated considerable expiratory prolongation and two (H. N. and F. L.) performed maximal voluntary ventilation in the high inspiratory position with a small tidal volume in a manner characteristic of pulmonary emphysema.

TABLE 3.—*Physiologic Findings Relative to Pulmonary Ventilation during Routine Pulmonary Function Study in 21 Patients with Rheumatic Heart Disease, Inactive*

Patient	Pulmonary ventilation, L./min./M² BSA, BTPS			Oxygen consumption, cc. per liter of ventilation, STPD	
	Rest	Exercise	Recovery 1	Rest	Exercise
Group I					
A. D.	3.7	13.1	10.8	40.7	59.2
J. S.	3.8	8.7	10.1	39.6	53.5
J. R.	5.2	11.6	21.9	27.4	44.3
M. R.	3.7	15.0	13.8	36.0	38.6
M. D.	6.8	14.6	16.8	25.5	25.2
H. R.	4.3	17.1	21.0	41.2	22.8
G. K.	3.6	12.6	10.3	40.3	48.1
N. W.	4.1	11.8	12.8	41.5	43.9
E. S.	5.0	14.6	17.2	36.9	36.7
E. C.	4.7	14.0	12.8	30.3	27.0
H. C.	—	10.6	13.1	—	39.0
V. H.	3.6	11.7	11.6	39.7	29.7
A. A.	3.7	13.1	10.8	37.1	27.4
L. A.	4.4	11.7	11.0	38.5	38.6
R. D.	4.6	9.2	10.2	37.6	38.3
A. B.	4.1	11.0	11.9	34.5	57.3
J. M.	4.3	12.3	9.9	40.5	56.0
G. M.	4.6	—	—	33.8	—
Group II					
H. N.	5.0	9.9	13.9	38.4	37.7
H. H.	3.9	15.0	12.5	35.6	23.7
F. L.	5.9	13.8	13.1	30.9	26.7

Abbreviations: L./min./M² BSA, BTPS = liters per minute per square meter of body surface area at body temperature and pressure, saturated with water; STPD = dry, 760 mm. Hg pressure, 0 centigrade.

4. Pulmonary Ventilation. The mean minute volume was slightly greater than normal at rest, during exercise, and in the recovery period in the patients comprising group I, (table 3, fig. 1). This hyperpnea was probably

true physiologic hyperventilation and not merely a manifestation of shallow breathing since arterial pCO_2* was not infrequently low after exercise as well as at rest. A reciprocal change in the oxygen consumption per liter of ventilation,† which was in keeping with this hyperpnea was also seen (table 3). Similarly, hyperventilation in relation to oxygen consumption was a feature of the performance of the group I patients and 10 other rheumatic subjects in a similar state of compensation during the mild steady exercise performed during cardiac catheterization, in which studies it was noted that the greatest degrees of relative hyperventilation were seen in those patients with the lowest cardiac outputs and the highest pulmonary arterial pressures (figs. 2*A* and 2*B*). Although the cause of the mild hyperpnea is unknown these findings are compatible with the suggestion[8, 12] that it may occur in response to increased activity of receptors sensitive to changes in tension within the pulmonary vessels or to changes in tension within the lung tissue itself. It is also possible, in view of the relation between cardiac output and ventilation, that factors related to the transport of oxygen, carbon dioxide, or other metabolites may exert an influence upon ventilation via pathways not specifically related to known elements regulating ventilation, that is, arterial anoxia, pCO_2, or hydrogen ion concentration. The ventilatory responses of the three patients in group II were essentially the same as that observed in the case of group I.

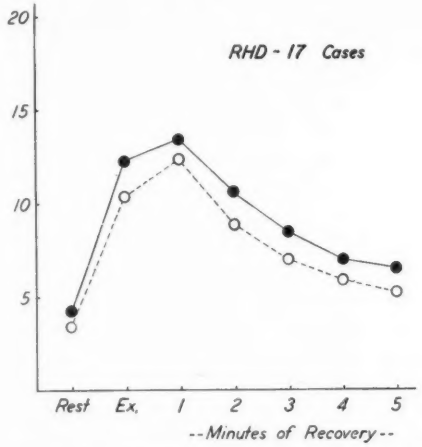

FIG. 1. Mean ventilatory response to the 30-step test of 17 patients with rheumatic heart disease. Dashed line and open circles indicate the mean response predicted for this group of patients.

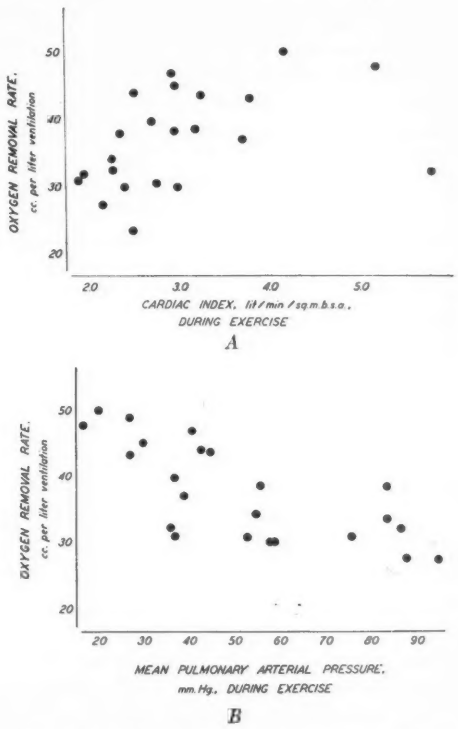

FIG. 2*A*. Relation of the oxygen removal rate (oxygen consumption per liter of ventilation) to the cardiac index during a steady exercise in a group of 19 patients with rheumatic heart disease. Twenty-two observations are included because three patients were studied before and after mitral commissurotomy.

B. Relation of the oxygen removal rate (oxygen consumption per liter of ventilation) to the mean pulmonary arterial pressure during a steady exercise in a group of 20 patients with rheumatic heart disease. Twenty-three observations are included because three patients were studied before and after mitral commissurotomy.

* pCO_2 equals the partial pressure of carbon dioxide in arterial blood.

† Comparison of ventilation among patients is facilitated by using this means which makes allowance for the small variations in the severity of the exercise, and hence oxygen consumption, which occurred.

5. Index of Intrapulmonary Mixing. The index of intrapulmonary mixing was normal in all but 2 of the 21 patients (table 2). One of the two (A. B.) was a young individual who was completely asymptomatic, while the other (H. H.) was a patient with restrictive fibrosis involving the right lung in addition to advanced rheumatic heart disease. Since, however, the majority of these patients were found to hyperventilate to some extent at rest it is recognized that certain degrees of uneven alveolar ventilation might well have escaped detection by this test.

6. Oxygen Consumption. Oxygen consumption was normal at rest in every case in group I, but was distinctly less than normal during the minute of standard exercise of the pulmonary function test in 6 of the 17 patients who were exercised (table 2). The low oxygen intake in the case of two patients (A. A. and R. D.) may be simply a reflection of subnormal physical exertion since only 22 and 24 steps were taken respectively by these patients instead of the usual 30. There was, however, no feature which clearly distinguished the four others, (M. D., H. R., V. H. and E. C.) from those with normal oxygen intakes except for the fact that each was found at another time to have a very low resting cardiac output, lower in each case than that found in any of the patients with normal oxygen consumptions during the standard exercise. The significance of this finding lies in the illustration it affords of the restriction which may be imposed by chronic rheumatic heart disease upon oxygen consumption during activity, in connection with which it should be noted that the level of resting cardiac output (or, rather, the resting arteriovenous difference) determines the extent to which oxygen consumption can increase with exercise just as does the ability to increase the cardiac output over the resting level.

Oxygen consumption was normal at rest in each of the three patients in group II, but it was definitely lower than normal during the period of standard exercise (table 2). In each case, however, there was inadequate physical exertion during the test.

7. Arterial Blood Gases. Arterial pCO_2 was normal or slightly low after exercise as well as at rest in every case in group I. Arterial oxygen saturation also was normal after exercise as well as at rest in the majority of these patients (table 2). A value of 92 per cent was noted at rest in one patient (M. D.), however, in whom the oxygen saturation after exercise was 89 per cent. Three other patients (J. R., R. D. and J. M.) were noted to have small drops in arterial oxygen saturation after exercise from values which were normal at rest.

The cause of this reduction in oxygen saturation with exercise is not known. It may be due to impaired diffusion of oxygen across the alveolar capillary membrane,[25] or simply a manifestation of normal physiologic shunts[26] in normal or moderately increased amount but with a low mixed venous oxygen content. In contrast to the findings of others,[25] however, there was no correlation between the level of arterial oxygenation and the degree of clinical disability found (tables 1 and 2). No effect, furthermore, of anoxia upon the degree of hyperventilation was noted.

One patient in group II (H. N.) was found to have appreciable arterial anoxia at rest and after exercise without evidence of carbon dioxide retention. The two others were normal in this respect (table 2).

Discussion

Among the many questions raised by these studies those pertaining to the origin of exertional dyspnea in the ambulatory rheumatic cardiac patient are of major interest since this is the foremost clinical manifestation of the disease.

It is apparent that the pulmonary functional pattern (as defined by these tests) of the 18 patients with uncomplicated heart disease differed greatly from that observed in the case of the patients with associated intrinsic pulmonary disease. Altered lung volumes, abnormal spirographic records, and reduced maximum breathing capacity in the latter group pointed out the presence of overdistention of the lungs and definite impairment of chest bellows action, functional patterns indistinguishable from those found in similar cases of chronic pulmonary disease without heart dis-

ease. On the other hand, there was nothing in the performance of the patients without intrinsic pulmonary disease to suggest the existence of abnormalities in pulmonary function which would be likely to result in exertional dyspnea. Although hyperventilation was noted at all stages of activity in these patients it was entirely too slight* in degree, even during exercise, to result in manifest ventilatory insufficiency. Factors, therefore, other than those relating to impaired ventilatory function must be concerned with the development of exertional dyspnea in these cardiac patients; and the major circulatory changes in chronic

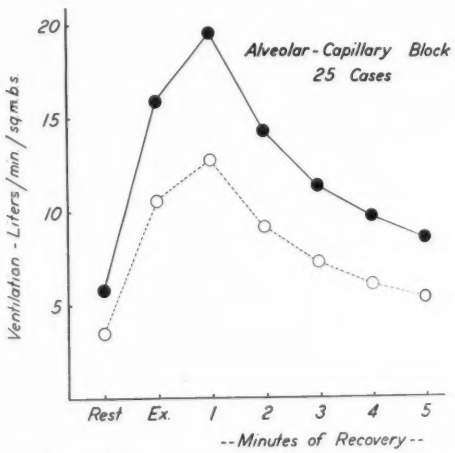

FIG. 3. Mean ventilatory response to the 30-step test of 25 patients with the syndrome of alveolar-capillary block. Dashed line and open circles indicate the mean response predicted for this group of patients.

rheumatic heart disease, that is, reduction in cardiac output and elevation of pulmonary vascular pressures, should be examined in this light.

A restricted ability to transport oxygen to and to remove metabolites from the skeletal muscles secondary to a low and relatively fixed cardiac output can be considered an important factor in limiting the work tolerance of patients with rheumatic heart disease for obvious reasons. Easy fatiguability, weakness, perhaps weight loss, seem likely to be related to this chronic reduction in blood flow; and in most patients the first two of these disturbances contribute greatly to the pattern of physical disability exhibited. Similarly, a limited cardiac output might conceivably result in labored breathing during exertion as a result of undue exhaustion of the respiratory muscles themselves despite the fact that in most circumstances the general manifestations of the reduction in blood flow could be expected to bring physical activity to a halt before such local influences become manifest. In the face, however, of possibly increased effort in breathing in the cardiac patient the "reserve" of the respiratory muscles might be impaired sufficiently to result in dyspnea at relatively low levels of minute volume. Studies on the work of breathing under various conditions will doubtless aid in solving this problem.

The importance of increased pulmonary vascular pressures in the production of dyspnea is equally ill defined. Although it has been shown that pulmonary hypertension per se does not bring about a reduction in vital capacity or maximum breathing capacity to any great extent, changes in pulmonary physical properties secondary to high pressures in the pulmonary veins, capillaries or arteries might still be important in the development of dyspnea. A reduction in pulmonary compliance secondary to increased intravascular pressure, for example, would necessitate increased energy expenditure in moving air into and out of the lungs which could certainly result in increased effort in breathing, a possible effect of which has been mentioned previously. Another possibility is that alterations in pulmonary elasticity might result in changes in the velocity of air flow at various phases of the respiratory cycle which may give rise to a sense of urgency to breathing not experienced by the normal individual at comparable minute volumes. Finally, pulmonary venous and arterial hypertension might conceivably lead to some form of distress, unrelated to the actual movement of air into and out of the lungs, as a result of

* The relative mildness of the hyperpnea seen in these patients is well brought out by comparison with that seen in a group of patients with the syndrome of alveolar-capillary block, a disorder in which hyperventilation is often of sufficient magnitude to tax ventilatory capacity[16, 27] (fig. 3).

stimuli arising in distended veins or arteries. The phenomenon of orthopnea suggests that some such mechanism may exist because discomfort noted in the supine but not in the upright position cannot be ascribed to ventilatory insufficiency as discussed herein despite the changes in lung volumes which occur with changes in posture.[28]

Thus the phenomenon of exertional dyspnea in these patients which seems not to be due to ventilatory insufficiency cannot be definitely attributed to any specific circulatory abnormality either, from such evidence as is now available. The relative importance of inadequate cardiac output and increased pulmonary vascular pressure in its development is not known, although there are various hypothetic mechanisms whereby each of these disturbances could result in dyspnea. Current studies of problems related to the mechanics of breathing will probably throw some light on the importance of effort or energy expenditure in breathing in this matter, a question which has been impossible to evaluate by means employed in the present studies, while examination of patients before and after successful mitral commissurotomy will perhaps aid in differentiating the influences of vascular congestion and inadequate cardiac output upon this wholly subjective yet clinically all important manifestation of heart disease.

Conclusions

1. Twenty-one patients with rheumatic heart disease and varying degrees of diminished cardiac reserve have been studied with respect to pulmonary and cardiocirculatory function. Eighteen of these were ambulatory individuals who presented no clinical signs of right ventricular failure or pulmonary edema despite the presence, in some instances, of advanced hemodynamic abnormalities secondary to heart disease. Three others had chronic pulmonary disease in addition to heart disease, but also, were not in congestive failure.

2. Although deviating slightly from normal in several respects the pattern of pulmonary function of the 18 patients without pulmonary disease or congestive failure does not account for the exertional dyspnea which these patients have. It suggests, rather, that dyspnea on exertion at the stage of cardiac insufficiency exemplified by this group of patients is a complex matter with multiple facets. Of these, weakness and easily induced fatigue of skeletal musculature including the muscles of respiration are possibly directly related to inadequacy of cardiac output while increased pulmonary vascular pressures may result in an increased effort in breathing as well as some form of subjective distress secondary to vascular distention per se.

3. In the absence of fluid retention, that is, of pulmonary edema, hydrothorax, or other evidences of this abnormality, or specific disease of the lungs, the presence of even severe degrees of pulmonary vascular engorgement may not result in appreciable alterations in the lung volumes, maximum breathing capacity and gross ventilatory response to mild exercise.

4. Intrinsic pulmonary disease, when it occurs concomitantly with compensated rheumatic heart disease, induces alterations in lung functions which may as a rule be readily differentiated from those due to heart disease alone.

Sumario Español

La función pulmonar y cardiocirculatoria se estudió en 21 pacientes ambulatorios con enfermedad reumática del corazón. Un patrón de función pulmonar se observó con desviación de un grado que es insuficiente para explicar la disnea esforzosa de estos pacientes. La patogénesis de este síntoma se discute en relación a las anormalidades cardiocirculatorias que a menudo fueron marcadas.

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A Critical Evaluation of the Hypotensive Action of Hydrallazine, Hexamethonium, Tetraethylammonium and Dibenzyline Salts in Human and Experimental Hypertension

By ALVIN P. SHAPIRO, M.D., AND ARTHUR GROLLMAN, PH.D., M.D.

The effects of hydrallazine and hexamethonium salts on blood pressure and related functions have been studied in a series of ambulatory and hospitalized hypertensive patients as well as in experimentally induced hypertension (rats and dogs). Comparative observations have also been made on the effects of tetraethylammonium chloride and Dibenzyline, a congener of dibenzylchlorethylamine (Dibenamine). Critical evaluation of the data indicates that the effectiveness of hydrallazine and hexamethonium salts, when used either alone or in combination, is not significantly greater in long term administration than that of previously existing regimens in the treatment of hypertensive vascular disease.

THE TREATMENT of hypertension by specific drug therapy has received renewed impetus with the introduction of potent sympatholytic agents. These have been advocated as a means of lowering the arterial blood pressure for prolonged periods of time, with consequent amelioration of the hypertensive vascular disease.[1-4] However, the level of the blood pressure in hypertensive patients varies considerably during the natural history of the disease and is influenced by a variety of nonspecific factors,[5-9] including changes in the psychodynamics of the individual's personality and the impact of the doctor–patient relationship.[9, 10] Moreover, the level of blood pressure, per se, is often an inadequate guide to the severity and progression of the vascular complications.[7, 8] These considerations emphasize the difficulty in establishing the ultimate value of hypotensive agents. Because of their widespread use and potential dangers,[11] a critical study of their effects was undertaken which incorporated certain principles minimizing the aforementioned difficulties.

METHODS AND MATERIALS

Three groups of patients were studied: (1) 10 outpatients with mild to moderately severe essential hypertension from the Hypertension Clinic of Parkland Hospital who were treated with hydrallazine chloride (Apresoline); (2) 12 hospitalized patients with hypertensive disease of varying severity treated with hexamethonium bromide and/or hydrallazine chloride; (3) 13 hospitalized hypertensive patients given intravenous injections of the drugs under study to evaluate their immediate effects. The clinical findings for the patients in each of the three groups are summarized in tables 1 through 3 respectively.

The 10 outpatients were seen by one investigator who determined all the blood pressures. Hydrallazine and a placebo were alternated in such a manner as to be entirely unknown to either patient or investigator. The daily dose was divided into three or four portions per day and office visits, at one or two-week intervals, were scheduled two or three hours after the last dose. An average of five blood pressure determinations at one-minute intervals, with the patient reclining, and an average of two determinations, with the patient standing, were recorded at each visit. Because of the nature of the study, the patients received considerably more attention by the physician than they had in their previous routine clinic visits. One patient died during the study and one discontinued therapy; the remaining eight were on drug or placebo for a total of 13 to 32 weeks.

In the hospitalized patients, drug–placebo alternation was known to the investigator, but not to the trained ward personnel who determined the blood pressures. Moreover, in the early phase of the study, even the fact that such alternation was contemplated was unknown to these individuals. Hexamethonium bromide and hydrallazine chloride in combination was given to eight patients, hydral-

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azine alone to three, and hexamethonium alone to one. Hydrallazine* was administered orally at 6 a.m., 12:00 Noon, and 6:00 p.m.; hexamethonium* intramuscularly at 9:00 a.m. and 9:00 p.m., with a 3:00 p.m. dose added later in most patients. One patient received both medications simultaneously at four hour intervals from 6:00 a.m. to 10:00 p.m. Each medication was started separately and carried either to the point of maximum effect or to the development of side-effects before the other was added. Further increments to one or both were then given if apparent diminution of the hypotensive action of the drugs developed. Placebos were substituted in a random manner, before, during, or after specific therapy. The blood pressures were recorded at regular intervals, with the patient reclining, from three to eight times per day and a daily average then determined. It has been our experience that variations in the "resting blood pressure"[12] from day to day are no less than those seen spontaneously during any given day; consequently, the daily average represents a reliable estimation of the day to day variation.

In the studies of acute effects, hydrallazine chloride, hexamethonium bromide and/or tetraethylammonium chloride (TEAC) and in three patients Dibenzyline (SKF 688A), were administered on consecutive days, in the order indicated in table 3. Five readings at one-minute intervals were determined with the patient reclining. The drug was then administered intravenously by direct injection, except on two occasions when Dibenzyline was administered as a constant infusion. Measurements of blood pressure were continued at one-half to one-minute intervals until the peak action of the drug had passed and the blood pressure had stabilized. The percentage fall in diastolic pressure was calculated from the lowest point reached by the diastolic blood pressure and the average of the five initial determinations. Usually the systolic blood pressure was also at its lowest at this time.

The studies on experimental hypertension were carried out on rats and dogs rendered hypertensive by the application of a figure-of-eight ligature to one kidney with removal of the contralateral organ.[13] The experimental procedures were identical to those used in previous studies in this laboratory.[14, 15] The blood pressures were determined on trained unanesthetized animals by the method of Kersten and co-workers[16] in the rats, and by puncture of the femoral artery and direct reading on a mercury manometer in the dogs.[17] In the rats, the drugs were administered by intraperitoneal injection or orally by admixture with the animals' food; in the dogs, the drugs were injected intravenously or intramuscularly or fed by enclosing the medication within a bolus of meat.

* Several patients had intravenous test doses of both agents prior to therapy, and one was treated with intravenous hydrallazine for five days.

Results

A. *Clinical Observations on the Human*

1. Outpatients Treated with Hydrallazine Chloride. The results obtained in each patient are summarized in table 1; representative protocols are illustrated in figure 1. In none of the patients did the blood pressure decrease significantly during periods on the drug. The alternating periods of drug and placebo revealed that elevations and declines in blood pressure were essentially unrelated to which preparation was being administered. In only one patient (M. E., fig. 1) were the blood pressures consistently lower during drug therapy, but the difference, as indicated in table 1, when all placebo and drug periods are averaged, amounts to only 9/8 mm. Hg. Among the entire group, the largest systolic difference was 13 mm. Hg in patient E. L.; the largest diastolic difference was 8 mm. Hg in patient M. E.

Pulse rates were consistently higher during the periods on drug therapy, ranging from 1 to 19 per minute (average, 6.4). Significant postural hypotension was not noted.

The gradual fall of the blood pressure during the early weeks of the experiment and in several instances throughout the course of observation was quite striking (patients M. F. and D. H., fig. 1). Comparison of the blood pressures on first visits with those on the last week of therapy indicated that these overall declines were usually of greater magnitude than those attributable to the drug (table 1).

All patients improved symptomatically during the course of the study, irrespective of whether placebo or drug was being administered. They "felt better" and expressed a relief of headaches, weakness, and fatigue. Even patient R. S., who had a duodenal ulcer in addition to severe hypertension and who died with rapidly progressive renal failure following the development of pyloric stenosis, had reported improvement prior to this terminal event.

The drug produced side effects which limited further increase in dosage in 8 of the 10 patients. These consisted chiefly of throbbing, pounding headaches, during which the patients felt flushed, frequently nauseated, and occasionally vomited. The maximum tolerated dose varied

from 75 to 350 mg. per day. Development of side effects was independent of the effect on the blood pressure. In at least two instances (patient D. R., on April 18, and patient M. F., on June 5, fig. 1) such symptoms appeared during the administration of placebo.

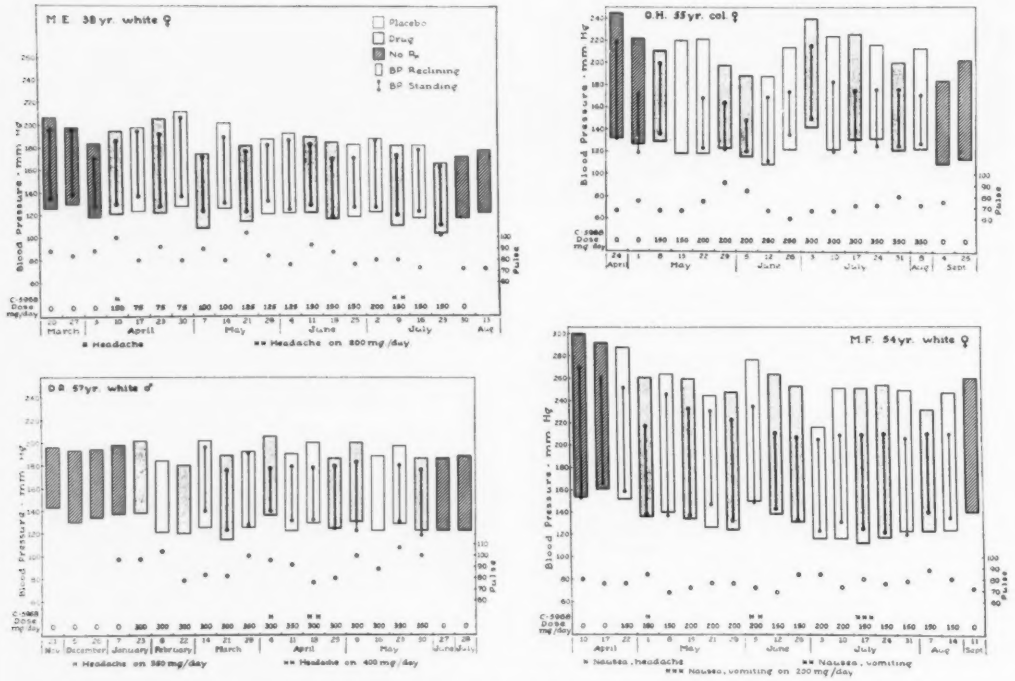

FIG. 1. The effect on blood pressure and pulse rate in four patients treated with oral hydrallazine (C-5968) in the doses indicated.

TABLE 1.—*Clinical Status and Blood Pressure Changes in Ten Ambulatory Hypertensive Patients Treated with Hydrallazine Chloride*

Patient	Age	Race/ Sex	Total PSP Output in 1 hour (per cent)	Urine Concentration Test (12 hours)	Blood Urea Nitrogen (mg. %)	Optic* Fundi	Cardiac Silhouette (+ indicates enlargement)	Average B.P. on Placebo (mm. Hg)	Periods on Placebo †	Average B.P. on Hydrallazine (mm. Hg)	Periods on Hydrallazine †	Difference (mm. Hg)	Average Pulse Rate Per Minute			Blood Pressure (mm. Hg)		
													on Hydrallazine	on Placebo	Difference	on First Visit	on Last Visit	Difference
M. L.	40	W M	50	—	13	I	−	174/127	3	173/130	3	1/−3	81	79	2	168/128	170/120	−2/8
D. R.	48	W M	50	1.015	17	II	−	193/125	7	193/126	7	0/−1	90	89	1	196/143	188/122	8/21
M. S.	54	N F	60	1.019	19	II	−	240/126	6	235/127	8	5/−1	87	83	4	234/136	223/130	11/6
J. R.	41	N F	65	1.022	10	II	−	196/121	7	204/119	7	−8/2	97	78	19	197/126	214/140	−17/−14
M. T.	38	N F	35	1.016	8	II	−	180/121	9	179/121	7	1/0	85	83	2	181/128	196/125	−15/3
R. S.	47	N F	35	1.014	25	III	+	258/150	3	271/153	2	−13/−3	94	92	2	258/149	268/143	−10/6
M. E.	34	W F	15	1.012	10	III	−	194/123	8	185/115	8	9/8	94	79	15	207/125	164/104	43/21
M. F.	54	N F	35	1.010	20	II	+	255/131	8	253/127	8	2/4	79	76	3	300/154	247/124	53/30
E. L.	21	N F	70	1.025	8	I	−	188/116	7	175/113	6	13/3	79	71	8	192/125	177/109	15/16
O. H.	55	N F	—	1.020	12	II	+	214/121	7	211/127	6	3/−6	77	69	8	245/132	213/122	32/10

* Keith-Wagener.

† Each period equals 7 to 14 days.

2. Hospitalized Patients. The clinical findings on admission of these 12 patients are presented

in table 2. Because of the variations in dosage and the different responses noted among patients in this group the results are presented individually rather than in tabular form. Representative cases are illustrated in figures 2 through 5.

1. R. M. See figure 2.

2. P. D. entered the hospital in the terminal stage of malignant hypertension with progressive hyponatremia and hyperkalemia. Blood pressure declined from 232/135 to 222/100 mm. Hg coincident with five days of therapy with oral hydrallazine in

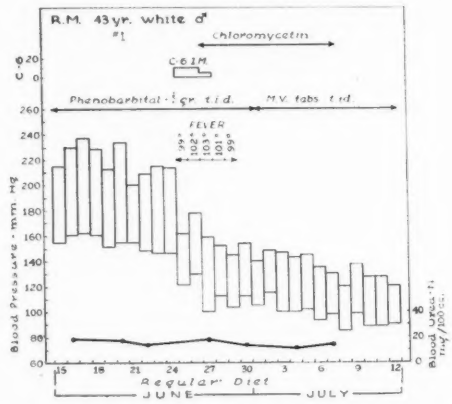

FIG. 2. R. M., with markedly elevated blood pressure on admission, but no evidence of renal or cardiac damage, was treated with hexamethonium bromide (C6) following an 11 day control period. Blood pressure declined markedly, but the drug was discontinued when he coincidentally developed bacillary dysentery (*Salmonella pullorum*). This responded promptly to antibiotics. No further specific therapy was given; nevertheless, blood pressure continued to decline, reaching normotensive levels.

a dosage of 300 mg. per day. He did not improve and died during treatment.

3. W. A., with grade IV fundi and moderate renal impairment, had a blood pressure on admission of 248/150 mm. Hg; the diastolic pressure fell to levels as low as 113 mm. Hg prior to treatment. With maximum doses of hydrallazine (300 mg. per day) continued for six weeks, and a low sodium diet, the diastolic pressure declined to as low as 103 mm. Hg but did not return to previous levels when placebo was substituted for the drug. Renal function and papilledema remained unchanged during therapy, although the patient improved symptomatically. Doses in excess of 300 mg. per day repeatedly induced nausea and vomiting.

4. M. M., with grade IV fundi and severely impaired renal function, was admitted in a comatose state following a convulsion. She regained consciousness following the intravenous injection of hydrallazine with a decline in diastolic blood pressure from 170 to 140 mm. Hg. The drug was then given orally in doses up to 800 mg. per day, at which point headaches were induced. Diastolic blood pressure, however, remained at 140 to 150 mm. Hg, was uninfluenced by addition of a low sodium diet, and continued at the same level when placebo was substituted after three weeks of therapy. It did rise to 160 to 170 mm. Hg later in her course when she was transferred to the Metabolic Ward. This was a rather infantile woman, insecure and dependent in her relationships with her physicians and in this new setting, where new and strange demands were made of her, increasing agitation became apparent. This subsided and the blood pressure declined again when the status quo was restored. Retinopathy gradually diminished during her hospitalization, despite only a slight decline in blood pressure.

5. E. F. See figure 3.

6. E. S. See figure 4.

7. E. C., with grade IV fundi but only moderate renal impairment, had a blood pressure of 228/150 mm. Hg on admission; within five days, the diastolic had fallen to a level of 98 mm. Hg while on a low sodium diet. The blood pressure then increased, despite continuation of the diet, to a diastolic level of 130 mm. Hg. With the administration of hexamethonium, the diastolic level ranged from 100 to 120 mm. Hg but this was not decreased further by the addition of hydrallazine, nor was it affected by a return to a regular diet. When the drugs were replaced by placebos after five weeks of combined therapy, the blood pressure rose slightly but remained below its initial levels and at the time of discharge had stabilized at 120 to 140 mm. Hg. Hexamethonium produced incapacitating postural hypotension in this patient, while headaches, which were present throughout his hospital stay, were aggravated by hydrallazine. The maximum tolerated doses of the drugs were 50 mg. and 450 mg. per day, respectively. Papilledema and retinal hemorrhages gradually subsided during his three month stay in the hospital.

8. D. T. manifested grade IV fundi but good renal function with blood pressure on admission of 220/170 mm. Hg. Diastolic level declined to 120 to 140 mm. Hg during two months of hospitalization during which he received five weeks of combined therapy with hexamethonium and hydrallazine in maximum doses of 100 mg. and 250 mg. per day, respectively. Urinary retention and headache prevented further dose increase. However, the diastolic had declined to 140 mm. Hg prior to onset of therapy and persisted at 120 to 140 mm. Hg when placebos were substituted. A low sodium diet while receiving both agents produced no further decrement. Retinal hemorrhages disappeared and papilledema partially

subsided during his hospital stay. Following discharge the blood pressure returned to preadmission levels, despite reinstitution of the combined drug therapy.

9. C. M. See figure 5.

10. G. W., with grade III fundi and minimal renal impairment had a blood pressure on admission of 244/162 mm. Hg. Hexamethonium and hydrallazine were administered up to a dosage of 100 mg. and 450 mg. per day, respectively, with further increase precluded by the development of postural hypotension. Diastolic blood pressure declined to 136 mm. Hg but then gradually rose to 143 to 154 mm. despite continuation of the maximum tolerated dose. When hexamethonium was replaced by placebos after four weeks of combined treatment the diastolic pressure remained at 133 to 159 mm. Hg; when all therapy was discontinued, and the patient continued on placebos, it varied from 142 to 162 mm. These manipulations accordingly produced insignificant changes in blood pressure; the lower levels, which were achieved early in the course, could not be maintained. A low sodium diet, instituted during several phases of his treatment, had no significant effect. Despite reinstitution of both drugs following discharge from the hospital, the blood pressure returned to its preadmission levels and progressive vascular damage developed.

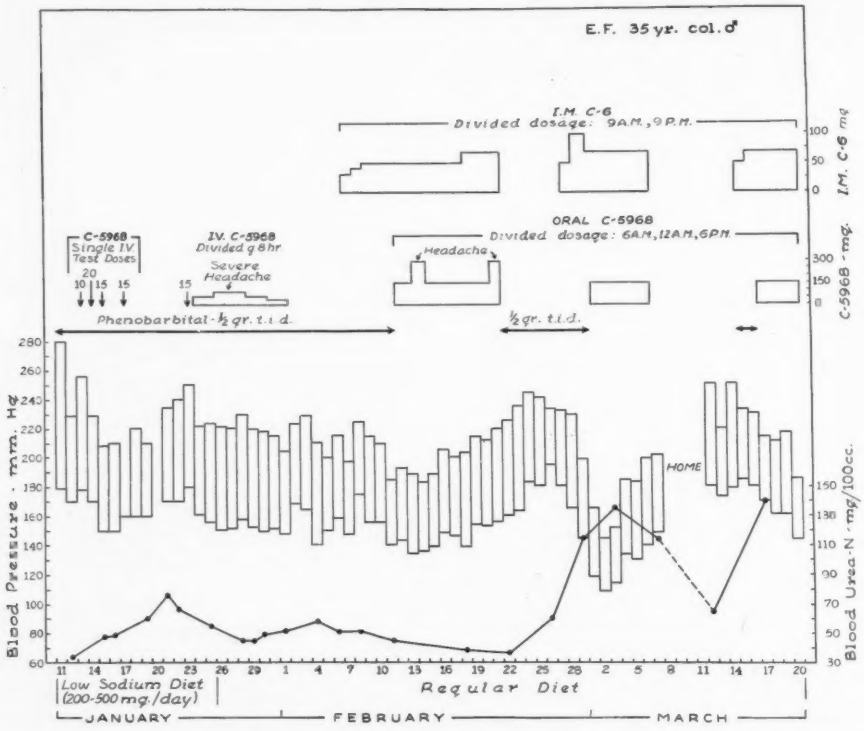

FIG. 3. E. F. entered the hospital with grade IV fundi accompanied by marked renal impairment. Initially, intravenous test doses of hydrallazine (C-5968) produced a marked although transient fall in blood pressure with relief of severe headache. When continued, intravenous hydrallazine induced severe headaches and had to be discontinued; nevertheless, blood pressure did not return to the high levels recorded on admission. When hexamethonium (C-6) and hydrallazine in combination were administered, the blood pressure declined temporarily, but severe headaches necessitated discontinuance of drug therapy, after which the blood pressure continued to rise. When the drugs were reinstituted, the blood pressure again declined; however, renal function deteriorated further as reflected in the rising blood urea nitrogen. After several days of absence from the hospital without therapy, during which time the blood urea nitrogen fell, therapy was reinstituted; the blood pressure declined, but renal failure progressed and the patient expired.

11. J. B., with severe impairment of renal function and grade II fundi, had a blood pressure on admission of 205/150 mm. Hg. This declined gradually with no specific therapy, reaching 190/118 mm. Hg three weeks after admission. The administration of hexamethonium and hydrallazine in doses up to 75 mg. and 450 mg. per day, respectively, induced no further decline in the blood pressure. Coincident with increasing anxiety about problems at home, the blood pressure rose to levels as high as those on admission despite continuation of therapy, and he left the hospital.

for hydrallazine there was a slight rise, but neither at this time nor following the discontinuance of placebos did it return to its initial levels.

3. Comparisons of Intravenously Administered Drugs. The pertinent data obtained with intravenous testing are given in table 3. There was no consistent increase in hypotensive effect with increasing doses of hydrallazine. In two patients (W. S. and F. M.), who received increasing doses of hexamethonium bromide, one

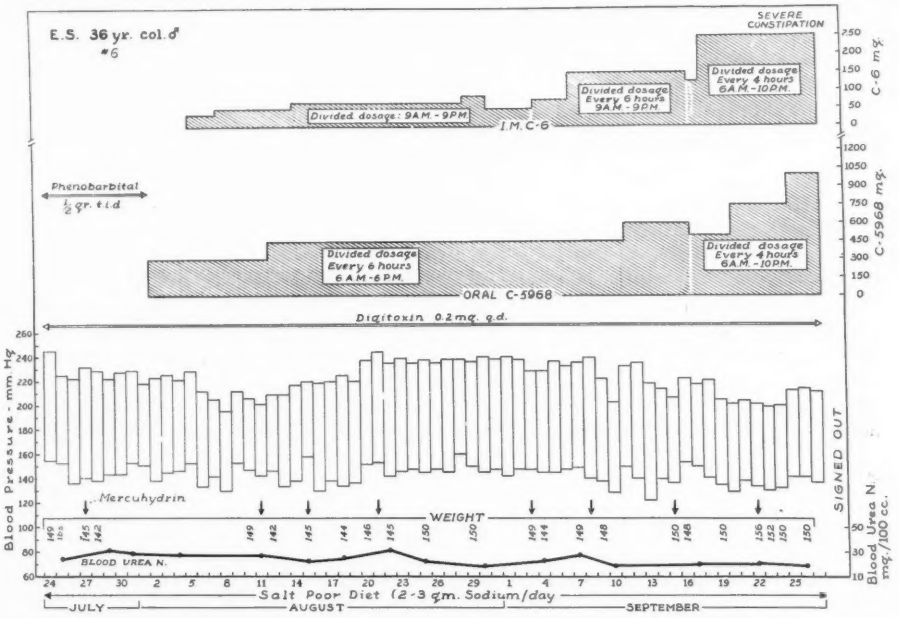

FIG. 4. E. S. with grade IV fundi and severe renal impairment was in congestive heart failure on admission. The latter was controlled with digitoxin and mercurials with a decrease in blood pressure. With hexamethonium and hydrallazine therapy, only a transient further decline occurred even when the dose was increased to 250 mg. and 1.0 Gm. per day, respectively, with both agents given simultaneously. Severe constipation was present at this dose level. Papilledema subsided and many of the retinal hemorrhages resolved during his hospital stay, despite the lack of appreciable decline of blood pressure. The effects could not be finally evaluated for he became increasingly resentful of the treatment and left the hospital.

12. D. P. had a fluctuant blood pressure, with diastolic levels ranging from 100 to 130 mm. Hg during the control period, no measurable renal impairment, and grade I fundi. On a combination of hexamethonium and hydrallazine in doses of 100 mg. and 150 mg. per day, respectively, the blood pressure declined to normotensive levels although wide daily fluctuations continued and postural hypotension was marked. When hexamethonium was discontinued and placebos substituted after ten days of combined therapy the blood pressure remained unaltered; when placebos were substituted

showed a further fall and one showed a slight decrease in effect. Patients tested with tetraethylammonium chloride were given only one injection of either 200 mg. or 400 mg. One patient (W. S.) received graduated doses of Dibenzyline with only a slight hypotensive effect which was not affected by the increase in dose, while two received single doses by infusion, again with only slight effects.

The time of maximum fall varied with the

drug administered. With hydrallazine, it averaged 19.6 minutes; with hexamethonium, 6.3 minutes; and with tetraethylammonium, 3.5 minutes.

Severity of the disease did not furnish any criteria by which the action of an individual drug or of a given dose could be predicted, nor did a consistent pattern of response emerge which might be related to the type of hypertensive mechanism.[2, 18] For example, in patients M. M. and D. H. a marked response to 20 mg. of hydrallazine occurred (60 per cent and 38

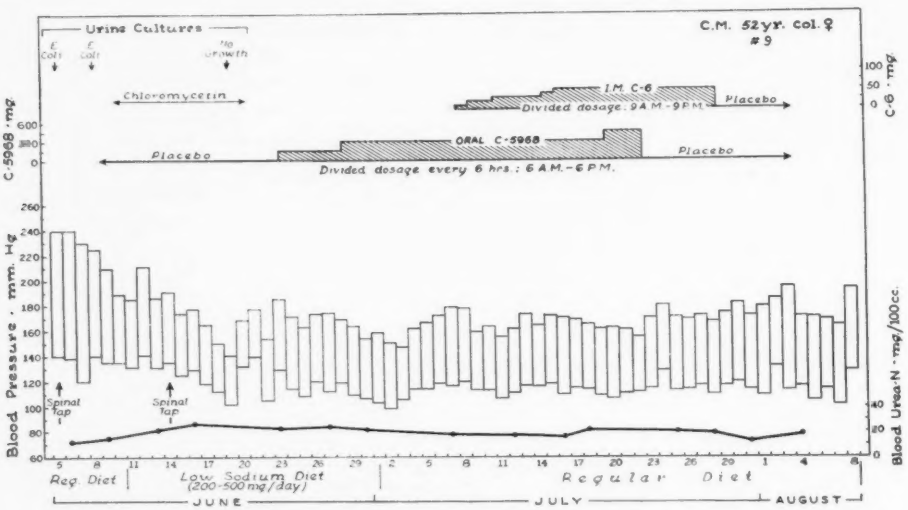

FIG. 5. C. M. with grade II fundi and moderate renal impairment displayed a striking decline in blood pressure when given placebos while on a low sodium diet and while being treated for a urinary tract infection. The addition of hexamethonium and hydrallazine in doses up to 50 and 450 mg. per day, respectively, caused no additional fall. The blood pressure which was 240/140 mm. Hg on admission, had declined by the time of discharge to 164/102 mm., although all specific medications had been discontinued 10 days previously and she had been on a regular diet for over one month.

TABLE 2.—*Clinical Status on Admission of Twelve Hospitalized Patients Treated with Hydrallazine and Hexamethonium*

Patient	Age	Race/Sex	Admission Blood Pressure (mm. Hg)	Fundi (Keith-Wagener)	Albuminuria	Blood Urea Nitrogen (mg.%)	Urine Concentration Test	Total PSP Excretion in 1 hour (per cent)	ECG*	Cardiac Silhouette (+ indicates enlargement)	Congestive Failure (0 to 3+)
R. M.	43	W M	215/155	II	0	15	1.022	60	N	0	0
P. D.	49	N M	232/130	IV	3+	184	—	—	LVP	+	3+
W. A.	56	W M	248/150	IV	trace	20	1.014	39	LVP	+	1+
M. M.	46	N F	260/170	IV	3+	28	1.015	30	LVP	+	0
E. F.	34	N M	280/180	IV	4+	34	—	5	LVP	+	0
E. S.	36	N M	245/155	IV	4+	24	1.010	20	LVP	+	3+
E. C.	58	W M	228/150	IV	1+	11	1.014	58	LVP	0	0
D. T.	34	W M	212/170	IV	trace	13	1.026	70	N	0	0
C. M.	52	N F	240/140	II	0	14	1.018	25	LVP	+	0
G. W.	39	N M	243/162	III	1+	13	1.020	58	LVP	0	0
J. B.	43	N M	205/150	II	trace	20	1.010	25	—	0	0
D. P.	33	W M	210/130	I	0	11	1.026	76	N	0	0

* N = Normal; LVP = Left Ventricular Preponderance.

per cent fall in diastolic pressure, respectively); yet quite different responses to 10 mg. of hexamethonium (0 per cent and 47 per cent, respectively) were elicited.

that none of the drugs under study exerted any detectable lowering of the blood pressure when administered either parenterally or orally. Only in excessive doses, beyond that

TABLE 3.—*The Effect of Intravenous Hydrallazine, Hexamethonium, and Tetraethylammonium Salts and Dibenzyline Chloride on the Blood Pressure of Hypertensive Patients*

Patient	Clinical Diagnosis*	Blood Pressure on Admission mm. Hg	Percentage Fall in Diastolic Blood Pressure														
			Hydrallazine Chloride (mg.)					Hexamethonium Bromide (mg.)				TEAC (mg.)		Dibenzyline (mg.)			
			10	15	20	25	30	5	10	15	20	200	400	5	10	15	‡
E. F.	M.H.	280/180	11.2	25.2	29.4			17.0				37.0					10.2
M. M.	M.H.	260/170	18.5	18.0	60.0†				0.0			5.0					16.1
W. S.	M.H.	220/156		10.3		30.1		6.5		5.3			10.4	8.1	5.7	6.6	
O. H.	B.E.H.	184/114			38.1				47.4			15.3					
P. D.	M.H.	232/130		12.0	18.0			4.3				7.0					
E. B.	B.E.H.	230/134			25.4	44.4		13.5					16.8				
J. B.	B.E.H.	205/150	7.2	13.4	16.2						3.2		4.0				
F. M.	M.H.	222/156	17.9		16.3	20.2		12.0		23.0		11.0					
A. M.	B.E.H.	160/120	8.3		17.4					13.8			14.5				
T. T.	B.E.H.	202/120		8.3		15.8				24.8			30.7				
E. S.	M.H.	220/150	17.3		19.2	20.0			16.2								
G. W.	M.H.	238/135		2.9								17.2					
M. S.	M.H.	242/142		14.9	11.7							25.0					

* B.E.H.: Benign Essential Hypertension; M.H.: Malignant Hypertension

† First dose administered in this patient

‡ E. F. received 25 mg. and M. M. 35 mg. by I.V. infusion in 5% D/W over a 2½ hour period.

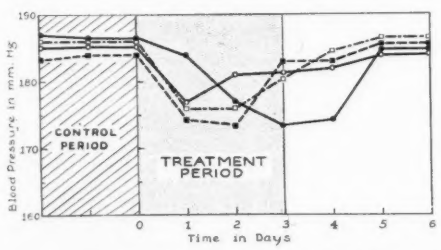

FIG. 6. The effect of the oral administration of hexamethonium chloride (○—○), hexamethonium bromide (■—■), and hydrallazine chloride (□—□) in doses of 100 mg. per kilogram of body weight and of Dibenzyline (●—●) in doses of 50 mg. per kilogram of body weight, on the average blood pressure of groups of six rats. The drugs were administered with the animals' food for four successive days (0 to 3 inclusive as indicated). More prolonged periods of medication resulted in death of the animals.

B. *The Effects on the Blood Pressure in Experimental Hypertension*

1. The Rat. Preliminary observations using doses (based on relative surface area) comparable to those used in the human indicated tolerated by the human, were declines in blood pressure noted, and under these conditions some of the animals died.

The results with oral administration are summarized in figure 6. It will be noted that on continued administration of these large doses the decline in blood pressure was only moderate and was not sustained.

2. The Dog. Results comparable to those obtained in the rat were also noted when the drugs were injected or administered orally to the hypertensive dog. In general, however, the dog was more reactive and more pronounced decrements in blood pressure were obtained with comparable doses based on the relative surface areas of the two species. Nausea and vomiting, however, were common concomitants of therapy and were observed when the blood pressure declined 30 mm. Hg or more.

The intramuscular injection of tetraethylammonium chloride in doses of 20 mg. per kilogram of body weight resulted in a maximum decline in the mean blood pressure varying from 0 to 30 mm. Hg in different animals with

a return to the pretreatment level within four hours. Administration of Dibenzyline in doses of 20 mg. per kilogram produced essentially the same results. Hydrallazine or hexamethonium chlorides injected intramuscularly or intravenously in doses of 2 mg. per kilogram resulted in a decline in mean blood pressure of 10 to 20 mm. Hg. When this dose was increased the decline in pressure was proportionately greater. The effect of giving the two drugs simultaneously resulted in an additive effect but no apparent synergism.

Discussion

The results which have been presented do not indicate any impressive hypotensive effects of hydrallazine or hexamethonium, alone or in combination, when administered in a carefully controlled manner. In hospitalized patients, significant declines in blood pressure which did occur during specific therapy persisted when placebos were substituted. Nor did clinical improvement necessarily coincide with the decline in blood pressure. In outpatients, treated with hydrallazine alone, the blood pressure often fell significantly during the course of several months of treatment, but alternation of drug with placebo revealed that the drug, per se, had minimal effects.

That these agents have immediate hypotensive effects, especially when given parenterally, is undisputed. On the other hand, the maintenance of hypotensive effects, which others have reported[1-4] and which were often noted in our patients, are not necessarily attributable to the action of drugs. Evaluation of long term administration must take into consideration other factors which will impinge upon the patient and influence the blood pressure.[9] Hospitalized hypertensive patients undergoing no specific treatment, for instance, regularly reveal a fall in blood pressure, even when malignant acceleration is present; precisely when such a decline will occur in relationship to the duration of hospitalization cannot be predicted.[19, 20] These effects of hospitalization are not simply a result of bed rest or relief from physical exertion; as a matter of fact, these patients whenever possible were encouraged to be ambulatory. Entrance into the hospital may constitute an escape from an emotionally stressful situation. A doctor–patient relationship which is reassuring and supportive may be developed; this is particularly true in an experimental study where special attention is given to the patient. These considerations apply equally to individuals treated on an outpatient status, especially when the administration of a new agent is associated with new enthusiasms and positive and supportive attitudes on the part of the physician.[9, 22]

Conversely, stress, including that produced by disturbances in the doctor–patient relationship, may counteract the hypotensive effects of any therapeutic regimen.[21-23] Such was apparent in patient J. B. whose family situation required his return to work, making hospitalization intolerable, and in patient M. M. from whom metabolic studies demanded cooperation which taxed her capacity so that hospitalization became threatening. Objections to the rigid regimen of treatment similarly affected the course in other patients both in the outpatient and hospitalized groups.

Side effects occurred frequently and constituted serious deterrents to continued therapy. These included postural hypotension, blurring of vision, urinary retention, and constipation with hexamethonium and headache, nausea, and vomiting with hydrallazine. The significance of side effects, however, must also be cautiously evaluated, as evidenced by the appearance of typical "hydrallazine headaches" in several instances during administration of placebos. Similarly, relief of symptoms which did not coincide with physical improvement was frequently noted.

Certain of the difficulties in evaluation imposed by the factors just discussed can be minimized by adequate control measures. The use of placebos, however, is of itself insufficient. As others have pointed out and as this study again emphasizes, their substitution should be unknown both to investigator as well as to subject.[24, 25] Moreover, parallel observations of the changing life situations and stresses acting on the patient are necessary, as are observations of the doctor–patient, or investigator–subject, relationship, since this represents an

important factor in the patient's current life situation while under treatment.[9]

The results on experimentally induced hypertension in rats and dogs, in whom a more objective evaluation of the direct effect of drugs on the blood pressure can be obtained, are in accord with our results in patients. Significant declines resulted only with doses much larger than tolerated by man. Such declines were not sustained with continued administration while about a third of the animals died when the treatment was extended beyond three or four consecutive days.

Our results thus indicate that the ultimate hypotensive effects of these agents are only slight or transient, when they are given in doses which can be tolerated. Sustained depressor effects which did occur were usually not attributable to pharmacologic activity, while clinical improvement did not necessarily coincide with decline in blood pressure. These considerations assume added significance in view of the dangers, particularly of deterioration of renal function, which exist with the indiscriminate use of hypotensive agents.

Summary

1. A critical study of the effects of hydrallazine and hexamethonium salts was carried out in three groups of hypertensive patients and on rats and dogs with experimental hypertension.

2. Ambulatory patients showed no appreciable change in blood pressure directly attributable to hydrallazine. More seriously ill patients treated in the hospital with hydrallazine alone or in combination with hexamethonium revealed only infrequent and transient declines in blood pressure directly induced by the drugs in doses which could be tolerated. Such clinical improvement as was elicited did not always correlate with observed depression of the blood pressure.

3. Comparison of the immediate effects of the intravenous administration of these drugs, as well as of Dibenzyline chloride and tetraethylammonium chloride, revealed no consistent or predictable patterns of response.

4. In evaluating the clinical effects of hypotensive agents, the need was emphasized for assessing other factors which are known to influence blood pressure and which cannot be completely eliminated from any study. This pertained particularly to the effects of hospitalization and the doctor–patient relationship.

5. A more objective evaluation of hydrallazine, hexamethonium, tetraethylammonium chloride, and Dibenzyline chloride was possible in the rat and dog with experimental hypertension. Here the results in the unanesthetized animal indicated appreciable depressor effects only when used acutely and in dosages several times as great as are tolerated by the human.

Acknowledgments

Several of the hospitalized patients were studied at the Veterans Administration Hospital, Dallas, Texas. We wish to express our appreciation to Drs. Seymour Eisenberg and Julian Acker of this institution for their invaluable aid in following these patients. The assistance of Dr. John Archer and Mrs. Marian Metsopoulos in the studies at Parkland Hospital is likewise gratefully acknowledged. Generous supplies of hydrallazine and placebos were supplied by Dr. F. L. Mohr and Ciba Pharmaceutical Products Inc.; hexamethonium salts were supplied through the courtesy of Dr. D. S. Searle and Burroughs, Wellcome & Co.; Dibenzyline was furnished by Dr. R. N. Buckley of Smith, Kline & French Laboratories.

Sumario Español

Los efectos de las sales de hydrallazine y hexamethonium en la presión arterial y funciones relacionadas han sido estudiados en una serie de pacientes hipertensos ambulatorios y aislados así como también en hipertensión inducida experimentalmente (perros y gatos). Observaciones comparativas también se han hecho sobre los efectos del cloruro de tetraetiloamonio y el Dibensyline, congénere del dibenciloclorоetilamina (Dibenamine). Evaluación crítica de los datos indica que la efectividad de las sales de hydrallazine y hexamethonium, cuando son usadas aisladamente o en combinación, no es significativamente mayor en el tratamiento por largo tiempo que el de los regimenes previamente existentes en el tratamiento de la enfermedad hipertenso vascular.

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The Hemodynamic Effects of Hypotensive Drugs in Man

IV. 1-Hydrazinophthalazine

By Edward D. Freis, M.D., John C. Rose, M.D., Thomas F. Higgins, M.D., Frank A. Finnerty, Jr., M.D., Robert T. Kelley, M.D., and Edward A. Partenope, M.D.

Further data are presented concerning the unusual hemodynamic effects of 1-hydrazinophthalazine. Previous observations demonstrating a marked increase in cardiac output in normotensive subjects are confirmed in hypertensive patients. The splanchnic vascular bed is one of the sites of increased blood flow. The similarity between the hemodynamic effects of 1-hydrazinophthalazine and pyrogens is pointed out and the pharmacologic basis for the clinically observed additive effects of 1-hydrazinophthalazine and hexamethonium is discussed.

Gross and his co-workers, in animals,[1] and Reubi, in man,[2] were the first to demonstrate that 1-hydrazinophthalazine (Apresoline) produces a reduction of arterial pressure and simultaneously an increase in renal blood flow. Since then considerable attention has been directed toward the further elucidation of the hemodynamic effects of this agent. Moyer and his associates, working with dogs, noted a marked increase in cardiac output and decrease in total peripheral resistance following administration of 1-hydrazinophthalazine.[3] This observation was confirmed in normal and hypertensive pregnant women by Assali and his co-workers using the ballistocardiographic method[4] and in normal subjects by Wilkinson and his associates using the intravenous catheterization technic (Fick).[5] Several of these investigators postulated that the total splanchnic vascular bed probably shares in the vasodilation.

In respect to blood flow through vascular areas other than the kidney, coronary blood flow was found to be increased in rabbits[1] and in the dog heart-lung preparation,[6] but has not been studied in man. Hafkenschiel and his associates in a preliminary report observed that blood flow through the cerebral vessels was essentially unchanged in man,[7] while skin blood flow as measured in the toes did not increase significantly.[8] In view of the apparently greater elevation of cardiac output than could be explained on the basis of the increases observed in renal and coronary flow, it seemed pertinent to determine the effects of 1-hydrazinophthalazine on blood flow through two other large areas, namely, the hepatic-portal (splanchnic minus renal and adrenal) vascular bed and the muscles, and to assess cardiac output changes in hypertensive patients.

Materials and Methods

The experimental procedures were carried out in hypertensive patients and normotensive subjects at Georgetown University Hospital and the Veterans Administration Hospital in Washington, D. C. Cardiac output, using the intravenous catheterization technic, and muscle blood flow in the calf, using a limb segment plethysmograph, were determined by methods described elsewhere.[9] The method of Bradley and his associates was used to estimate hepatic-portal blood flow.[10] All determinations were carried

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Supported in part by research grants from Ciba Pharmaceutical Products, Summit, New Jersey, the National Heart Institute, U. S. Public Health Service, and the Squibb Institute for Medical Research, New Brunswick, N. J.

Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

out in the postabsorptive state. The peripheral blood samples were taken from the femoral artery.

1-Hydrazinophthalazine was rapidly administered, usually intravenously, in a dose of approximately 0.25 mg. per kilogram of body weight. During the 6 cm. above the level of the skin of the patient's back. The zero point used for pressures in the right auricle, ventricle and pulmonary artery was 5 cm. below the angle of the sternum. During the determinations of muscle blood flow the arterial pressure

TABLE 1.—*Effect of 1-Hydrazinophthalazine on Mean Arterial Pressure, Cardiac Output and Total Peripheral Resistance*

Patient and Diagnosis	Sex	Age	Surface Area	Control				After 1-Hydrazinophthalazine					
				Mean Arterial Pressure	Cardiac Rate	Cardiac Output	Total Peripheral Resistance*	Dose I.V.	Time after Drug	Mean Arterial Pressure	Cardiac Rate	Cardiac Output	Total Peripheral Resistance
			sq. M.	*mm. Hg*	*per min.*	*liters per min.*	*units*	*mg.*	*min.*	*mm. Hg*	*per min.*	*liters per min.*	*units*
C. L.	M	42	1.93	92	76	6.0	.0153	28	10	73	120	7.9	.0092
Cushing's syndrome				94	78	5.9	.0159		20	63	116	8.5	.0074
W. E.	M	46	2.09	125	65	4.2	.0298	34	15	117	84	10.3	.0114
Ess. hyper.				128	64	4.8	.0267						
A. B.	F	53	1.35	200	104	7.0	.0285	16	20	155	125	15.2	.0102
Ess. hyper. & anemia				187	100	7.5	.0249		32	143	125	10.3	.0139
C. M.	M	50	1.91	152	80	6.3	.0242	25	12	132	115	11.6	.0114
Ess. hyper.									24	132	130	10.1	.0131
W. G.	M	60	1.78	218	129	4.9	.0445	20	8	200	140	11.6	.0172
Malig. hyper.				236	123	5.9	.0400		21	148	130	12.4	.0119
C. L.	M	47	1.66	176	100	4.4	.0400	21	15	152	115	9.7	.0157
Ess. hyper.				184	100	5.0	.0368		23	144	130	12.7	.0114

* $\frac{\text{M.A.P. in mm. Hg}}{\text{C.O. in ml. per min.}}$

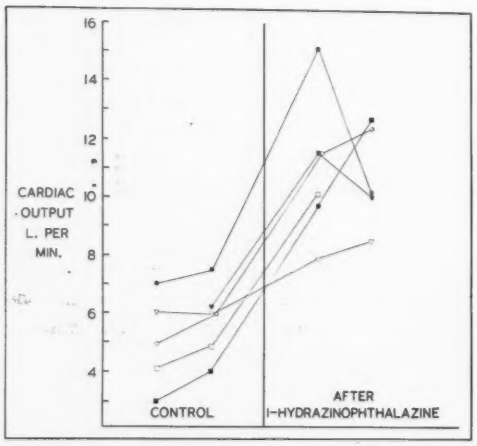

FIG. 1. Chart showing elevations of cardiac output following 1-hydrazinophthalazine in six hypertensive patients.

estimation of hepatic blood flow and cardiac output, arterial pressure was measured directly in the femoral artery, using a strain gage as described elsewhere.[9] The pressure in the hepatic vein was measured similarly, the zero point being placed at a level

was recorded in the brachial artery by the standard auscultatory method.

RESULTS

I. Cardiac Function and Total Peripheral Resistance

The cardiac output increased markedly in all of the six hypertensive patients studied (table 1, fig. 1), the average maximum increase over the control values being 128.2 per cent, S.D. 77.4. The average decrease in mean arterial pressure at this time was 28.4 per cent, S.D. 10.7. There was no correlation between the degree of increase in cardiac output and the extent of the blood pressure reduction. The mean decrease in total peripheral resistance was 62.1 per cent, S.D. 8.3. The heart rate increased in all cases, the mean increase being 32.1 per cent, S.D. 16.6. The average increase in stroke volume was 45 per cent.

The right auricular pressure was determined in two instances and increased from 1 to 2 mm. Hg in one instance and from 1.5 to 2 mm. Hg in the other. The mean pulmonary arterial pres-

sure also increased in two patients studied. In one it rose from a control value of 13 to 17 mm. Hg and in the other from 11 to 18 mm. Hg.

patic blood flow. In the remaining six cases which included three patients with essential hypertension, two patients with malignant hy-

TABLE 2.—*Effects of 1-Hydrazinophthalazine on Arterial Pressure and Estimated Hepatic-Portal Blood Flow*

Patient and Diagnosis	Sex	Age	Surface Area	Control			After 1-Hydrazinophthalazine				
				Mean Arterial Pressure	EHBF	Peripheral Resistance	Dose I.V.	Time after Drug	Mean Arterial Pressure	EHBF	Peripheral Resistance
			sq. M.	*mm. Hg*	*ml. per min.*	*units*	*mg.*	*min.*	*mm. Hg*	*ml. per min.*	*units*
W. W.	M	54	1.89	160	960	.167	35	12	130	2030	.064
Ess. Hyper.				160	910	.176		17	130	1755	.074
				160	1028	.156		22	126	1486	.085
E. G.	M	53	1.75	140	699	.200	24	8	110	910	.121
Ess. Hyper.				140	1020	.137		13	110	788	.140
				130	1126	.116		19	110	654	.168
A. P.	M	45	1.58	160	845	.190	19	13	120	1634	.073
Ess. hyper.											
M. H.	M	50	1.64	170	1292	.132	20	7	132	1755	.075
Ess. hyper.				170	1256	.135		13	120	1433	.084
L. J.	M	33	1.73	195	1555	.125	20	10	160	2208	.073
Malig. hyper.				190	1818	.105		17	150	2148	.070
J. Mc.	M	38	1.82	160	1126	.142	24	6	126	1243	.101
Malig. hyper.				170	1142	.149		11	100	1450	.069
				180	1035	.174		16	90	2028	.044
L. F.	M	30	1.75	107	873	.123	24	4	96	1871	.051
Normal				105	1075	.098		11	105	1358	.077

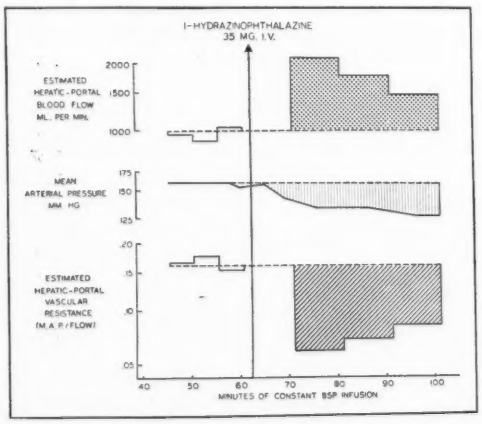

FIG. 2. Chart showing elevation of estimated hepatic-portal blood flow and reduction of mean arterial pressure and estimated hepatic-portal vascular resistance in W. W., a white male, age 54, with essential hypertension.

II. Estimated Hepatic-Portal Blood Flow

One patient with essential hypertension exhibited no significant change in estimated he-

pertension and one normal subject, there was considerable increase in hepatic-portal blood flow (table 2, fig. 2). The maximum increase over control values ranged between 31 and 110 per cent (mean 75 per cent, S.D. 32). During the period of maximum change in estimated hepatic-portal flow the mean arterial pressure decreased between 9 and 47 per cent (mean 23 per cent, S.D. 13). It was apparent, therefore, that a marked decrease in hepatic-portal vascular resistance had occurred.

The hepatic venous pressure was measured in three patients. In two cases the pressure in the hepatic vein rose from 8 mm. Hg before 1-hydrazinophthalazine to 11 mm. Hg after, and in the remaining case it rose from 10 to 11 mm. Hg.

III. Blood Flow in the Calf (Muscle Blood Flow)

Calf blood flow was determined in seven subjects three of whom were hypertensive and four normotensive. In six of these cases which included all of the hypertensive patients there was a moderate decrease in blood flow ranging

between 3 and 24 per cent (mean 15 per cent). In the remaining normotensive subject there was an increase in muscle blood flow of 14 per cent. Since, in most instances, both arterial pressure and blood flow decreased there probably was little or no change in vascular resistance in the calf segment following 1-hydrazinophthalazine.

TABLE 3.—*The Effect of 1-Hydrazinophthalazine on Arterial Pressure and Blood Flow in the Calf*

Patient and Diagnosis	Sex	Age	Control		After 1-Hydrazinophthalazine			
			Arterial Pressure	Blood Flow per 100 ml. Limb Volume	Dose I.V.	Time after Drug	Arterial Pressure	Blood Flow per 100 ml. Limb Volume
			mm. Hg	*ml. per min.*	*mg.*	*min.*	*mm. Hg*	*ml. per min.*
R. G.	M	53	235/115	6.26	24	15	180/90	5.40
Ess. hyper.			235/115	6.41		28	190/95	5.77
			235/115	7.81		45	190/95	6.45
						59	200/100	5.06
L. C.	M	57	190/125	5.99	25	7	160/115	4.41
Ess. hyper.			195/125	5.13		10	170/110	4.37
			185/125	4.88		13	170/115	4.36
R. Mc.	M	50	230/140	3.71	20	7	190/110	3.14
Ess. Hyper.			230/142	4.40		10	190/104	2.80
						14	190/106	3.50
						18	190/106	2.75
						22	190/106	3.62
						26	190/104	3.29
						39	195/104	3.78
J. F.	M	29	120/78	2.65	24	13	115/55	2.74
Pneumonia (convalescent)			120/78	2.76		20	120/55	2.49
			128/70	3.55		33	125/55	1.95
						52	115/55	1.91
J. B.	M	29	120/60	2.82	22	11	115/45	2.56
Hodgkin's Disease			120/55	3.37		26	110/45	2.43
			120/55	3.50		41	115/50	3.82
						56	115/60	3.60
J. H.	M	27	120/75	9.14	14	2	120/60	7.67
Bronchial asthma			120/65	8.50		13	120/55	7.99
						33	110/60	8.33
						35	110/60	8.33
						55	120/75	7.88
T. B.	M	30	120/80	2.96	30	15	125/55	5.13
Normal			120/80	3.65		30	130/60	3.32
						40	130/60	2.45
						55	130/60	4.17

DISCUSSION

1-Hydrazinophthalazine is the only hypotensive agent studied thus far in which the reduction of blood pressure is associated with a significant increase in cardiac output. The increase is accompanied by a tachycardia and a more forceful action of the heart clearly visible under the fluoroscope or by observing the apex impulse. The increased circulatory rate is not shared by the entire body since the muscles, brain[7] and skin[8] show no appreciable change in blood flow, but is directed primarily through the total splanchnic vascular tree including the kidneys.[1, 2] However, Fazekas recently has found marked increases in cerebral blood flow after Apresoline.[17]

An increased venous return is suggested by the slight but definite elevation of hepatic-portal venous pressure, right auricular pressure and pulmonary arterial pressure. As a result of the augmented cardiac output after 1-hydrazinophthalazine, the systolic pressure falls less than with other hypotensive agents; whereas,

because of the marked decrease in total peripheral resistance, the diastolic pressure falls considerably more than the systolic.

This pattern of hemodynamic response is similar to that observed during the pyrogenic reaction. Here also, as demonstrated by Bradley, there is a reduction of arterial pressure in hypertensive patients accompanied by marked increases in cardiac output and hepatic-portal and renal blood flows.[11] Bradley has shown in addition that these hemodynamic responses are not dependent on activation of the temperature center, per se, since they occur when the febrile response is blocked by administering aminopyrine. The site of action of pyrogen in producing these hemodynamic responses is unknown, but it seems possible that it may be similar to the site of action of 1-hydrazinophthalazine. In this connection Gross and his coworkers believe that the drug acts centrally.[1]

It has been reported from this laboratory[12] as well as by Schroeder[13] that 1-hydrazinophthalazine and hexamethonium have an additive hypotensive effect. The hemodynamic responses to these agents lend support to this clinical impression. Hexamethonium usually decreases cardiac output as well as right auricular and pulmonary arterial pressures.[9] Thus, the combination of markedly decreased peripheral resistance following 1-hydrazinophthalazine and decreased right heart pressures and cardiac output after hexamethonium may have a powerful additive effect in reducing systemic arterial pressure. Moyer has shown in dogs that the increase in cardiac output following 1-hydrazinophthalazine is prevented if hexamethonium is given concurrently.[14]

The hemodynamic effects of 1-hydrazinophthalazine differ radically from those produced by other hypotensive agents thus far studied. For example, in patients with compensated hearts the cardiac output remains unchanged after veratrum viride[15] or dihydroergocornine[16] and usually decreases slightly after hexamethonium.[9] Following veratrum there is a generalized rather than regional decrease in peripheral resistance, while after hexamethonium marked vasodilation occurs only in the distal extremities. Following dihydroergocornine there is an increased resistance in the hepatic-portal area. After all of these agents (except 1-hydrazinophthalazine) renal blood flow and glomerular filtration rate decrease at least transiently.[9, 15, 16] Thus, it seems evident that each of these hypotensive drugs differs somewhat from the others in its effects on blood flow through various areas.

The ideal agent for the treatment of essential hypertension would be one which restores blood flow to normal in those areas in which it has been reduced and which does not disturb otherwise the normal distribution of blood flows or cardiac output. In respect to its ability to increase renal blood flow 1-hydrazinophthalazine would appear to be ideal, but the drug also markedly increases cardiac output to levels which often are above the physiologic range for resting subjects.

Summary and Conclusions

1-Hydrazinophthalazine administered to hypertensive and normotensive subjects produced the following hemodynamic effects:

1. The cardiac output increased markedly in hypertensive patients despite a definite reduction in mean arterial pressure. The calculated total peripheral resistance fell sharply.
2. Estimated hepatic-portal blood flow also increased significantly.
3. Blood flow through the muscles (calf segment) usually decreased slightly.
4. The similar hemodynamic patterns produced by 1-hydrazinophthalazine and pyrogen are noted and the pharmacologic basis for the clinically observed additive effects of 1-hydrazinophthalazine and hexamethonium is discussed.

Acknowledgments

The authors wish to thank Miss Jean Pietras, Miss Barbara Allison, Mr. Victor Landi and Mr. Larry C. Gaskins for valuable technical assistance.

Sumario Español

La observación de que el 1-hydrazinophthalazine aumenta marcadamente la producción total cardíaca se comprueba y además se demuestra que la circulación calculada hepato portal aumenta con la droga. La circulación de la pantorrilla generalmente disminuye

ligeramente. La similaridad entre las respuestas hemodinámicas al 1-hydrazinophthalazine y pirógenos se indica.

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Further Observations on the Effects of Autonomic Blocking Agents in Patients with Hypertension

I. General Systemic Effects of Hexamethonium, Pentamethonium, and Hydrazinophthalazine

By DAVID GROB, M.D., AND HERBERT G. LANGFORD, M.D.,
WITH THE ASSISTANCE OF BARBARA ZIEGLER

Hexamethonium and pentamethonium produced a greater reduction in blood pressure in patients with malignant hypertension who had low serum concentration of sodium or severe encephalopathy than in those with benign hypertension. Concurrent administration of hydrazinophthalazine resulted in an additive effect on the blood pressure of most patients, with slower development of tolerance and less marked postural hypotension. In many patients there was improvement in signs and symptoms attributable to hypertension. Harmful effects of reduction in blood pressure occurred mainly in patients with malignant hypertension and consisted of renal insufficiency and evidence of myocardial and retinal ischemia.

HEXAMETHONIUM and pentamethonium [bis - trimethylammonium hexane (C-6) and pentane (C-5)] are quaternary ammonium compounds which are capable of blocking the transmission of nervous impulses across autonomic ganglia, both sympathetic and parasympathetic.[1, 2] This action results in reduction in the blood pressure of recumbent hypertensive subjects, and of erect normotensive and hypertensive subjects.[3-5] The daily oral or subcutaneous administration of these compounds is followed by some reduction in the blood pressure of most hypertensive patients and symptomatic improvement in many of these, but the degree and duration of this effect is limited by the development of tolerance.[6-8] The concurrent administration of another antihypertensive drug, 1-hydrazinophthalazine (Apresoline),[9] has been reported to have a synergistic effect, and to facilitate reduction of the blood pressure.[10, 11] Pentamethonium and hexamethonium have also been administered to normotensive subjects in order to increase blood flow to the extremities of patients with peripheral vascular disease,[5, 12] to reduce the secretion of gastric acid,[13] and to produce postural hypotension and reduction of hemorrhage during certain operative procedures.[14]

The studies to be reported here describe the effects of hexamethonium and pentamethonium administered intravenously to 72 hypertensive patients, and orally for several weeks to 30 of these. The effects of hydrazinophthalazine administered orally to 24 hypertensive patients, and in conjunction with hexamethonium to 16 of these for several months are also described. The effect of intravenous hexamethonium and pentamethonium on the blood pressure of 30 normotensive subjects is also reported.

PROCEDURE

The hypertensive patients who were studied varied in age from 18 to 64 (average 42) years. The known duration of hypertension was 1 to 30 (average 6) years. All the patients had symptoms attributable to hypertension. The patients who are classified as having malignant hypertension are those who had marked and sustained elevation of blood pressure, and some degree of renal insufficiency, papilledema,

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Presented in summary at the scientific session of the Twenty-fifth Annual Meeting of the American Heart Association, Cleveland, Ohio, April 19, 1952.

and hypertensive encephalopathy. The range and average of the age and known duration of hypertension were approximately the same for the patients with benign and malignant hypertension.

In the large majority of observations the dichloride salts of hexamethonium and pentamethonium were employed, and in a smaller number the dibromide or di-iodide salts. The effective dose of these salts was dependent on the amount of methonium ion, and their effects were the same except for the occurrence of symptoms attributable to the accumulation of bromide ion in the few subjects who received protracted administration of the dibromide salt. The doses of methonium compound that are recorded are of the dichloride salt.

All observations on hypertensive patients were preceded by a period of at least one week of bed rest in the hospital. The methonium compounds were injected intravenously at an average rate of 3 mg. per minute until the blood pressure had fallen to normal or to levels intermediate between the original and normal, or until 108 mg. had been administered. The amount injected varied from 4 to 108 mg. (average 42 mg., or 0.6 mg. per kilogram). The blood pressure was determined by auscultation at intervals of one half to one minute during injection, and until the maximum fall was attained, after which measurements were made at longer intervals until the blood pressure had returned to near the original level. At varying intervals after injection, the effect of sitting, with the legs dangling over the sides of the bed, and of standing, was observed. Changes in posture were always active, rather than passive. Hexamethonium was administered orally several days after the intravenous injection, in an initial dose of 0.125 or 0.25 Gm., repeated at 8- to 12-hour intervals. The dose was progressively increased at intervals of one or more days by increments of 0.125 Gm., and the interval between doses shortened to six and then four hours, in an effort to maintain some degree of reduction in the blood pressure. The maximum daily dose was 9 Gm. In a few patients the effects of orally administered hexamethonium and pentamethonium were compared.

Several days after the cessation of hexamethonium, and after return of the blood pressure to the original elevated levels, hydrazinophthalazine was administered orally, in an initial dose of 25 mg., repeated at eight hour intervals. The dose was progressively increased at daily intervals by increments of 25 to 50 mg., and the interval between doses shortened to six and then four hours, in an effort to maintain some degree of reduction in the blood pressure. The maximum daily dose was 1 Gm. While the patients were receiving hydrazinophthalazine in average daily dose of 350 mg., hexamethonium was added, in an initial dose of 0.125 or 0.25 Gm. three times a day. The dose of hexamethonium was then gradually increased at intervals of one to several days in an effort to lower the blood pressure to normal or intermediate levels. This occurred at a daily dose of hexamethonium of between 0.7 and 6 Gm. (average 2.3 Gm.). The two drugs were administered at the same time and, whenever possible, before meals. In a few patients the sequence of drug administration was reversed.

All observations were carried out in the hospital, except for 10 patients who were given hexamethonium and hydrazinophthalazine for one to three months in the hospital, and were then followed in the outpatient department. During the patients' hospitalization the blood pressure, recumbent, was usually recorded prior to each dose of drug, and that recumbent and erect two hours after drug administration at least twice during the day. Following discharge from the hospital this was recorded from three times a day to once a week.

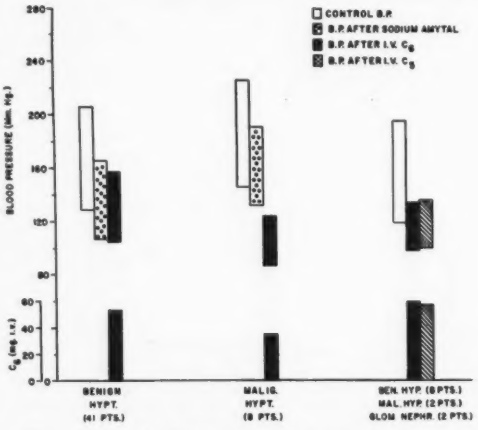

FIG. 1. Effect of intravenous hexamethonium on the blood pressure of patients with benign and malignant hypertension, and comparison with effect of Sodium Amytal–induced sleep and pentamethonium.

RESULTS

Effect of Intravenous Hexamethonium on Blood Pressure (Figs. 1 and 2)

Patients with Benign Hypertension. The intravenous administration of 10 to 108 mg. (average 53 mg.) of hexamethonium to 41 patients with benign hypertension resulted in a reduction in the blood pressure, recumbent, to normotensive levels in 20 patients, to near normotensive levels (within 20 mm. Hg) in 11, and to levels intermediate between the original and normotensive in 8. In two patients there was no reduction in blood pressure following 108 mg. of hexamethonium. There was a

rough parallel between the effect of hexamethonium, in the doses administered, and the reduction in blood pressure that occurred during Sodium Amytal-induced sleep, except that the former was slightly greater in most patients. However, in two patients whose blood pressure did not fall during sleep, hexamethonium reduced the pressure to near normotensive levels. The effect of hexamethonium on the blood pressure was detectable within two or three minutes after injection of each increment, and was maximal within an average of nine minutes after the conclusion of the injection. In five patients the blood pressure fell appreciably during the half hour after termination of the injection. More rapid administration than 3 mg. per minute resulted in a somewhat greater reduction in blood pressure in most patients. In some patients increasing the dose of drug beyond that necessary to lower the blood pressure to normotensive levels resulted in only a slightly greater reduction in pressure, suggesting that a blood pressure "floor" had been reached, but in most patients a significantly greater fall in pressure occurred. In one patient progressive increases in the dose of hexamethonium resulted in lowering of the recumbent pressure to 95/56 mm. Hg. When hexamethonium was injected in equal doses on several occasions, there was usually some variation in the extent of the fall in blood pressure. The fall in systolic pressure was more rapid and about twice as great as the fall in diastolic pressure. The reduction in pressure was accompanied by only a slight increase in cardiac rate from an average of 87 to 94 per minute. In all patients there was marked postural hypotension, the pressure falling to an average of 104/76 after one half to two minutes of standing, with the systolic pressure falling more rapidly than the diastolic. The postural hypotension was accompanied in most patients by symptoms of syncope, including giddiness, sometimes nausea, vertigo, scotomata, tinnitus, faintness, pallor, deep sighing respirations, and yawning. Postural hypotension also occurred after the injection of small doses of drug which had little or no effect on the pressure, recumbent. The marked reduction in blood pressure that occurred on standing was accompanied by only slight acceleration of cardiac rate, to an average of 101 per minute, which was only slightly greater than the average rate on standing prior to hexamethonium (98 per minute). When the recumbent position was resumed the blood pressure rose immediately to, or slightly above, the level prior to standing, and the cardiac rate became slightly slower than the rate prior to standing. The pressure, recumbent, gradually returned to the initial level over a period of 2 to 24 (average 5) hours, while the postural hypotension diminished more slowly (average duration 7 hours). The length of time that the patients could stand before the blood pressure fell varied with the time that had elapsed since the injection of drug.

Patients with Malignant Hypertension. The intravenous administration of 5 to 80 mg. (average 29 mg.) of hexamethonium to eight patients with malignant hypertension resulted in a reduction in pressure to below normal in two patients, to normal levels in four, to near normal in one, and to a level intermediate between the original and normotensive in one. In all except the latter patient, the fall in pressure was considerably greater than that which had occurred during sodium amytal induced sleep. Reduction in blood pressure to shock levels was accompanied by an increase in average cardiac rate of 20 per minute, and lesser reduction in blood pressure by an average increase of 5 per minute. In six patients marked fall in pressure was accompanied by symptoms of syncope. The blood pressure increased slightly on elevation of the lower extremities, and returned to or near the original level over a period of three to nine (average five) hours. Marked postural hypotension was present in all the patients when they were allowed to sit or stand up following partial recovery of the blood pressure, recumbent.

Patients with Chronic Glomerulonephritis and Hypertension. The intravenous administration of 10 mg. of hexamethonium resulted in a marked reduction in pressure to below normal in one patient, while the administration of 50 mg. to another patient resulted in a moderate reduction, to normal. In the former patient the reduction in pressure was much greater than that which occurred following sodium

Amytal, while in the latter it was slightly greater.

Influence of Nitrogen Retention, Low Serum Sodium Concentration, Low Dietary Intake of Sodium, and Presence of Hypertensive Encephalopathy on Effect of Intravenous Hexamethonium. None of the patients with benign hypertension had nitrogen retention, low serum sodium concentration, or encephalopathy, and none had a drastic fall in blood pressure, recumbent, following the intravenous administration of less than 85 mg. of hexamethonium. All of the eight patients with malignant hypertension had nitrogen retention and encephalopathy, and six of them had a marked fall in

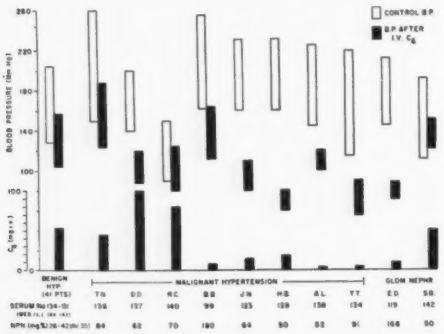

FIG. 2. Effect of intravenous hexamethonium on the blood pressure of patients with benign and malignant hypertension, and with glomerulonephritis; correlation of effect with serum sodium concentration, and lack of correlation with blood nonprotein nitrogen concentration.

blood pressure, recumbent, following the injection of less than 18 mg. of hexamethonium (fig. 2). Of these six patients, four had low serum sodium concentration. The other two patients were distinguished only by the presence of the most marked encephalopathy observed in this group. Of two patients with chronic glomerulonephritis and uremia who were studied, one, whose serum sodium concentration was low, was extremely responsive to a small dose of hexamethonium, while the other patient, whose serum sodium concentration was normal, showed a relatively small response to a much larger dose. The effect of hexamethonium appeared to be prolonged in the patients with renal insufficiency, but increased response to a single injection was observed only when the renal insufficiency was associated with low serum sodium concentration or severe encephalopathy.

When the daily dietary intake of sodium chloride was increased from 1 to 4 Gm. in one of the patients with malignant hypertension who had a low serum sodium level and a marked response to a small dose of hexamethonium, there was a striking diminution in response to the drug, coincident with an increase in the serum sodium level (fig. 3). In two patients with benign hypertension the response to hexamethonium or pentamethonium was increased following reduction of sodium chloride intake and injection of mercurial diuretic, although the serum sodium level was not altered (fig. 3). The response was also considerably increased following onset of subarachnoid hemorrhage in one other patient and of cerebral vascular accident, with coma, in another.

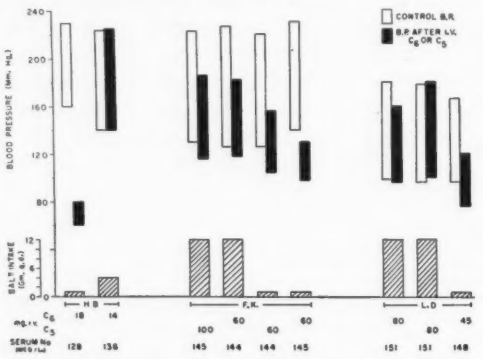

FIG. 3. Influence of sodium chloride depletion and restitution on the effect of intravenous hexamethonium and pentamethonium on the blood pressure of one patient with malignant hypertension (H. B.) and two with benign hypertension. Patient H. B. was given increased intake of sodium chloride for 15 days, patient F. K. decreased intake for five and six days, and patient L. D. decreased intake for five days, prior to redetermination of effect of hexamethonium or pentamethonium on the blood pressure. The latter two patients received 2 cc. of Thiomerin i.m. on the first and fourth days of salt restriction.

Normotensive Subjects. The intravenous administration of 20 to 50 mg. (average 30 mg.) of hexamethonium produced a slight to moder-

ate reduction in the blood pressure, recumbent, by 8/0 to 40/20 mm. Hg (average 21/10) in 29 of 30 subjects. This was accompanied by an average increase in cardiac rate of 8 per minute. On standing there was a marked fall in blood pressure within one to three minutes, to 80/60 or below, with syncope. The cardiac rate increased only slightly on standing by an average of 6 per minute. The effect of resuming the recumbent position, and the duration of the postural hypotension, were similar to that observed in the hypertensive subjects.

In one normal subject the intravenous injection of 25 mg. of hexamethonium at 3 mg. per minute resulted in a fall in the blood pressure, recumbent, from 130/90 to 70/50. The cardiac rate did not change. The blood pressure was not altered by elevation of the lower extremities. The administration of 0.25 mg. of adrenaline subcutaneously resulted in transient elevation of the blood pressure to 240/100, but within 10 minutes the pressure was again subnormal. Following 20 mg. Vasoxyl (methoxamine hydrochloride[15]) intramuscularly the blood pressure gradually returned to the original level over a period of 40 minutes. Injection of 0.25 mg. of adrenaline several weeks later had little effect on the blood pressure.

Effect of Oral Hexamethonium on Blood Pressure (Fig. 4)

Patients with Benign Hypertension. The response to the initial oral doses paralleled in general the response to approximately one-twentieth as much drug administered intravenously, and also paralleled roughly the response to sodium amytal. During the first four days of oral administration of 0.5 to 3 (average 1.3) Gm. a day the blood pressure, recumbent, fell to normal levels in three patients, to near normal in five, and to intermediate levels in eight. The systolic pressure was usually reduced to a greater extent than the diastolic. In two patients there was no reduction in recumbent pressure. The average blood pressure declined from 213/126 to 167/103. In 16 of the 18 patients there was further reduction in pressure on standing to, or below, normotensive levels. The postural hypotension diminished with activity or following the application of an abdominal binder or of pressure bandages to the lower extremities. It was most marked on motionless standing immediately after getting up from the recumbent position or following exercise. Most patients had to lie down at times because of syncope. There was considerable fluctuation in the blood pressure, both recumbent and erect, during a 24-hour period, even when hexamethonium was administered at four hour intervals. The average cardiac rates, recumbent and erect, were the same as prior to hexamethonium administration (80 and 98 per minute).

During 1 to 25 weeks (average 4 weeks) of administration of hexamethonium the response

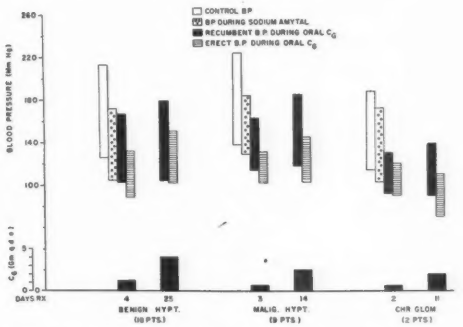

FIG. 4. Effect of oral administration of hexamethonium on the recumbent and standing blood pressure, and comparison with effect of Sodium Amytal-induced sleep on the recumbent pressure.

to the drug gradually diminished, and the daily dose had to be increased to an average of 4 Gm., and as high as 9 Gm. in two patients, in order to maintain any reduction in the blood pressure. Two patients continued to have no reduction in blood pressure while recumbent, in spite of increased intake of drug. The blood pressure, recumbent, was maintained at normal levels in only one patient, near normal in three, and at intermediate levels, particularly with regard to the systolic pressure, in six. It returned to the original level in six patients. The average blood pressure, recumbent, during the fourth week of drug administration was 179/104. Postural hypotension disappeared in two patients, increased in two, and diminished in the remainder. In eight patients, the erect

blood pressure continued to be at or near normotensive levels, while in eight patients it was intermediate between the original and normotensive. The pressor response to cold, emotional stimuli, and intravenous histamine was only slightly to moderately diminished, and elevation of the blood pressure to hypertensive levels occurred following these stimuli. In one patient who developed tolerance to large oral doses of hexamethonium there was a marked decrease in the response to large intravenous doses of either hexamethonium or pentamethonium (fig. 5). The response returned between 4 and 17 days after cessation of

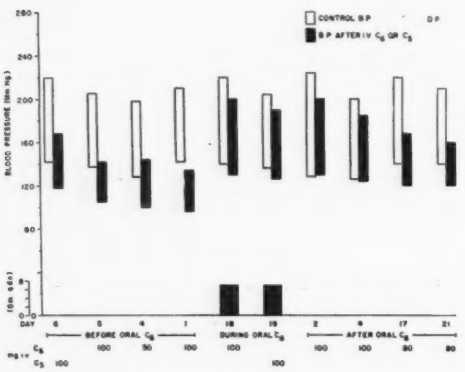

FIG. 5. Development of tolerance to large intravenous doses of hexamethonium and pentamethonium in a patient with benign hypertension after 18 and 19 days of oral administration of hexamethonium, and return of reactivity after cessation of oral administration.

oral administration. The development of tolerance to hexamethonium was also observed following intramuscular administration at six hour intervals for periods of 3 to 10 weeks. Moderate response to the drug returned within seven days after cessation of administration.

Patients with Malignant Hypertension. The initial reduction of blood pressure was somewhat greater in most of these patients than in those with benign hypertension, the blood pressure falling in response to smaller doses of hexamethonium. This paralleled their response to intravenous hexamethonium (in doses about one twentieth as great), and was, in most instances, considerably greater than their response to sodium amytal. Four patients had a marked reduction in pressure to or near normotensive levels during the first three days of oral administration, five patients had reduction to levels intermediate between the original and normotensive, and one patient had no reduction in pressure.

Of the patients who had the greatest initial response to small oral doses of hexamethonium, two had low concentration of serum sodium, and these two patients and two others had the most marked hypertensive encephalopathy. In spite of their initial responsiveness to small oral doses of hexamethonium, and in spite of the presence of low serum sodium concentration and of hypertensive encephalopathy, tolerance to the drug appeared in the malignant hypertensives just as rapidly as in the patients with benign hypertension. During the first two weeks of daily oral administration the blood pressure rose progressively, in spite of a four fold increase in the daily dose of hexamethonium. In four patients the blood pressure returned to the original levels, while in four it rose to levels intermediate between the original and normotensive. Alterations in the erect blood pressure and in recumbent and erect cardiac rates were the same as in the patients with benign hypertension.

Patients with Chronic Glomerulonephritis. The response to oral hexamethonium paralleled that to intravenous administration (fig. 2) in the two patients who were studied. One patient (S. B.), who had low concentration of serum sodium, had a marked reduction in blood pressure to below normal after only 0.12 Gm. of hexamethonium orally. The other patient had a moderate reduction in pressure to normal levels, and moderate postural hypotension, during a 10-day period of oral administration of 1 to 2 Gm. of hexamethonium daily.

Effect of Pentamethonium on Blood Pressure

Intravenous pentamethonium had the same effect as hexamethonium in both normal and hypertensive subjects (fig. 1). Oral pentamethonium had slightly less effect on the recumbent and erect blood pressure than hexamethonium. The development of tolerance to either drug was accompanied by tolerance to the other.

whether administered orally or intravenously (fig. 5).

Potentiation of the Hypotensive Effect of Other Vasodilator Drugs by Hexamethonium

During the daily oral administration of hexamethonium or pentamethonium there was an increase in the hypotensive effect of other vasodilator drugs, such as nitroglycerin, erythrityl tetranitrate, and hydrazinophthalazine, administered orally. The effect of the former two drugs and hexamethonium on the recumbent and erect blood pressure was more than additive, while the effect of hydrazinophthalazine and hexamethonium was usually additive (figs. 6 and 7).

Lack of Correlation between the Effect of Methonium and of Lumbodorsal Sympathectomy on Blood Pressure

Six patients who had received intravenous hexamethonium or pentamethonium were later subjected to lumbodorsal sympathectomy. In five of these, the recumbent blood pressure was reduced to or near normotensive levels by methonium, while the sixth patient had no fall in pressure following 108 mg. of hexamethonium. All had marked postural hypotension. Two weeks after sympathectomy the recumbent pressure of all six patients was at or near normal levels, and all had marked postural hypotension. Nine months later the recumbent pressure of five patients had returned to or near the original level, while that of one patient remained normal. Three patients had normal pressure on standing, while in three the pressure fell to levels intermediate between the hypertensive recumbent level and normal.

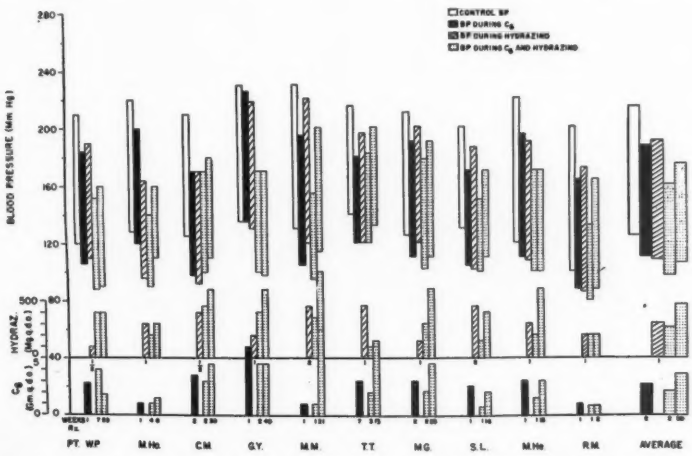

FIG. 6. Effect of oral administration of hexamethonium, hydrazinophthalazine, and hexamethonium plus hydrazinophthalazine on the blood pressure of 10 patients with benign hypertension.

Effect of Sympathectomy on Response to Hexamethonium

Hexamethonium was administered intravenously and orally to four patients (two with benign and two with malignant hypertension) prior to lumbodorsal sympathectomy, and one half, one, two, and three years after sympathectomy, at which time the recumbent blood pressure had returned to or near the original level. The initial response of these patients to hexamethonium was greater following sympathectomy, but the rate of development of tolerance appeared to be unchanged.

Effect of Oral Hydrazinophthalazine on Blood Pressure (Figs. 6 and 7)

This drug was administered to 16 patients with benign hypertension and eight with malignant hypertension for an average period of 12 days. The doses that were administered resulted in a moderate reduction of recumbent

pressure in 14 patients (9 benign and 5 malignant hypertensives) to levels intermediate between the original and normotensive, and no significant reduction in 10 patients. In two patients with malignant hypertension the blood pressure fell transiently to near normal.

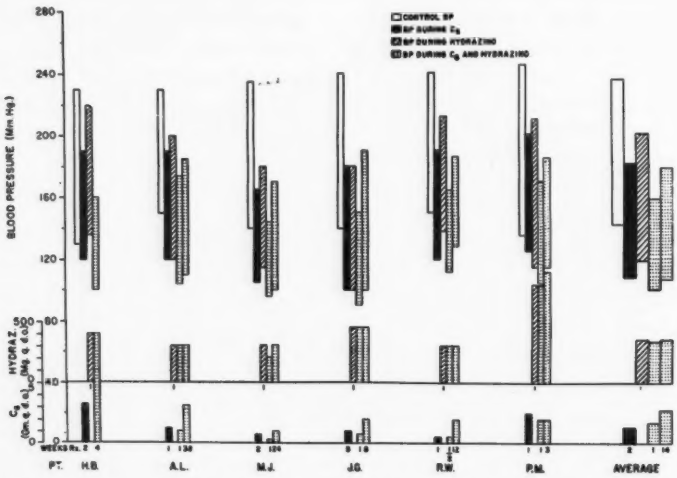

FIG. 7. Effect of oral administration of hexamethonium, hydrazinophthalazine, and hexamethonium plus hydrazinophthalazine on the blood pressure of six patients with malignant hypertension.

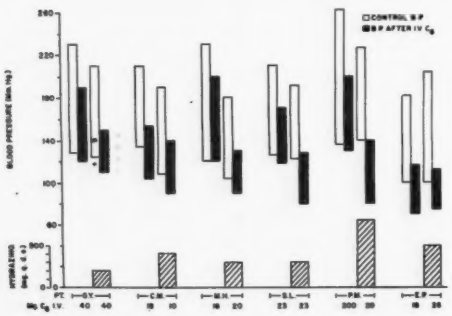

FIG. 8. Effect of intravenous injection of hexamethonium on the blood pressure of five patients with benign hypertension and one with malignant hypertension (P. M.) before and during the administration of oral hydrazinophthalazine.

In the patients with benign hypertension the average blood pressure fell from 212/129 to 183/109, and in the malignant hypertensives from 235/142 to 198/120. In some instances the reduction in diastolic pressure was almost as great as in systolic pressure. There was no correlation with the reduction in blood pressure that occurred during Sodium Amytal–induced sleep. The average pressure, erect, was only slightly lower than that recumbent, and marked postural hypotension was not observed. In some patients the effect of the drug on the blood pressure diminished during the brief period of observation, but this development of tolerance was less marked than following hexamethonium. Hydrazinophthalazine produced slight to moderate cardioacceleration, even in some of the patients who had little or no fall in blood pressure, the average rate increasing from 86 to 97 per minute. On standing the average cardiac rate increased to 110 per minute.

Effect of Oral Hydrazinophthalazine on Blood Pressure Response to Intravenous Hexamethonium (Fig. 8). Hexamethonium was administered intravenously to five patients with benign hypertension and one with malignant hypertension before and during the daily oral administration of hydrazinophthalazine. In five patients whose blood pressure had been lowered to some extent by oral hydrazinophthalazine, the blood pressure was reduced to lower levels by intravenous hexamethonium than had been the case prior to hydrazinophthalazine administration. In two patients the effect on

the blood pressure was additive, while in three others it was more than additive. The potentiation of the hypotensive action of hexamethonium by hydrazinophthalazine was most marked in the patient with malignant hypertension. In the sixth patient, whose blood pressure rose slightly during hydrazinophthalazine administration, the pressure fell to the same normotensive level after each injection of hexamethonium.

alone produced a moderate lowering of blood pressure to levels intermediate between the original and normotensive in eight patients (four benign and four malignant), and a slight reduction in eight patients. All but two of the patients had mild or moderate postural hypotension. Hydrazinophthalazine alone produced a moderate or slight lowering of pressure in the same number of patients. Concurrent administration of the two drugs resulted, during the

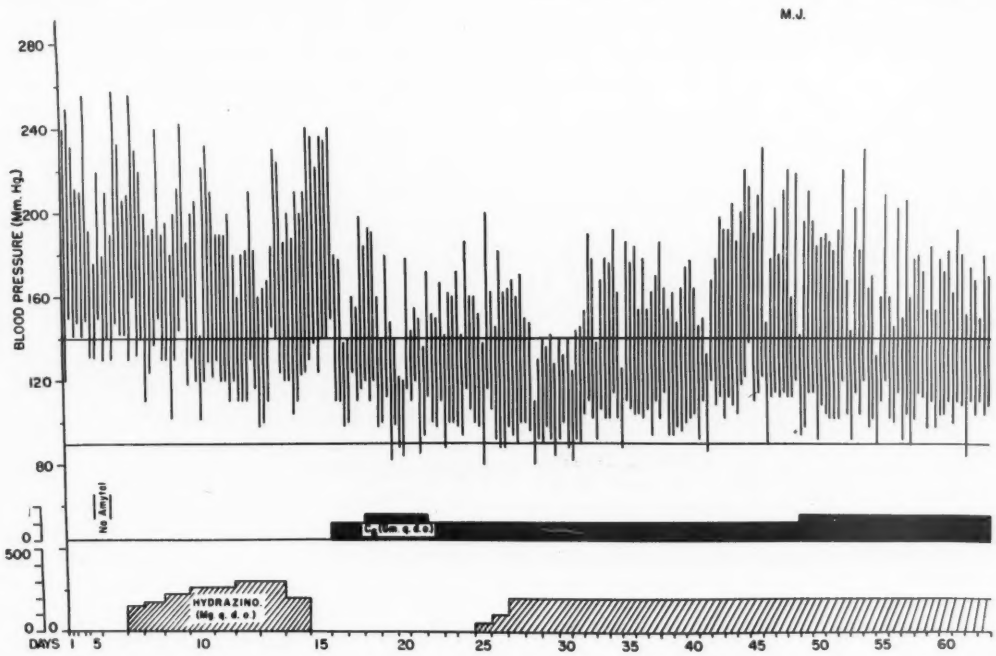

FIG. 9. Effect of Sodium Amytal-induced sleep, oral hydrazinophthalazine, oral hexamethonium, and hexamethonium plus hydrazinophthalazine on the recumbent blood pressure of a patient with malignant hypertension.

Effect of the Concurrent Oral Administration of Hydrazinophthalazine and Hexamethonium on Blood Pressure (Figs. 6, 7, 9 and 10)

This was studied in 10 patients with benign hypertension and six with malignant hypertension, following a period of observation of the effect of hexamethonium and of hydrazinophthalazine administered separately. The former drug was usually administered first, in order to allow a sufficient time interval between the two courses of hexamethonium for tolerance to this compound to diminish. Hexamethonium

first two to four weeks, in reduction in the blood pressure, recumbent, to or near normotensive levels in eight patients (five benign and three malignant), and to levels intermediate between the original and normotensive in eight patients (five benign and three malignant). In the patients with malignant hypertension smaller doses of drugs were required to lower the pressure than in those with benign hypertension. The reduction in systolic pressure was greater than the reduction in diastolic pressure. With continued administration for 2 to 40

(average 18) weeks the blood pressure rose to a moderate degree in eleven patients, in spite of an average increase of 60 per cent in the daily dose of both hexamethonium and hydrazinophthalazine. In three patients the blood pressure returned to near the original levels, while in 12 patients the blood pressure was maintained at levels intermediate between the original and normotensive. The development of tolerance was slower and less marked than during the administration of hexamethonium alone. In most patients there were fairly wide fluctuations in blood pressure throughout the day (fig. 9); it was not unusual for the blood pressure to be normotensive at some times, and near the original elevated level at

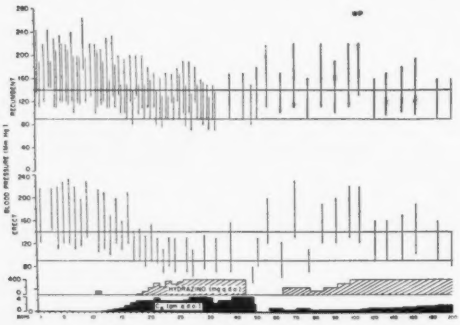

FIG. 10. Effect of oral hydrazinophthalazine, hexamethonium, and hexamethonium plus hydrazinophthalazine on the recumbent and standing blood pressure of a patient with benign hypertension.

other times, especially following emotional stress. The response to the cold pressor test was only slightly diminished. In four patients the response to the drugs increased after several weeks, and the dose of hexamethonium had to be reduced (fig. 10). All the patients had moderate or severe postural hypotension during the first week of addition of hexamethonium to hydrazinophthalazine. This was most marked immediately on rising from the recumbent position, and usually diminished on walking about. With continued administration of these drugs the postural hypotension diminished in severity in all patients, and disappeared in 10, except for brief periods following increases in the intake of hexamethonium. In four patients postural hypotension recurred following exercise, sweating, or diarrhea, or during very hot weather. One patient had no postural hypotension while he was engaged in office work, but did have this when he relaxed at home. In general, postural hypotension was less marked during combined drug administration than during hexamethonium alone, and the same degree of postural hypotension was usually accompanied by a somewhat greater increase in cardiac rate, and by less marked symptoms of syncope. Nevertheless, it was very difficult, even in the more responsive patients, to lower the recumbent blood pressure to normotensive levels without producing intermittent syncope on standing.

During hydrazinophthalazine administration less hexamethonium was required for comparable reduction in pressure than when hexamethonium was administered alone. The effect of combined administration of the drugs on the blood pressure was approximately additive in 12 patients, greater than additive in two, and less than additive in two.

When administration of the drugs, or of their combination, was discontinued postural hypotension disappeared within one to two days and the recumbent blood pressure rose within two to five days to or above the original level. When drug administration was resumed, smaller doses were initially required for reduction of the blood pressure than at the time of cessation of administration.

The degree of lowering of the blood pressure could not be correlated with the dietary intake of sodium chloride, which was 1 to 4 (average 3) Gm. a day. When tolerance to hexamethonium or to hexamethonium plus hydrazinophthalazine had developed the dietary intake of sodium chloride was reduced in some patients, to as low as 0.5 Gm. a day. In several instances, prolonged restriction of sodium chloride intake increased the response to drug administration to some extent, and appeared to delay, though it did not prevent, the development of tolerance.

Cardiac Rate. The average cardiac rate was 78 (recumbent) and 87 (erect) during the control period and during hexamethonium administration, 93 and 105 during hydrazino-

phthalazine, and 87 and 101 during combined drug administration.

Effects of Reduction in Blood Pressure by Oral Hexamethonium, Hydrazinophthalazine, and Hexamethonium Plus Hydrazinophthalazine

Effect of Signs and Symptoms Attributable to Hypertension (*Table 1*). The degree of amelioration of the signs and symptoms attributable to hypertension depended in part on the degree and duration of the reduction in blood pressure, and was more notable following combined drug administration than following either drug alone. Improvement occurred after moderate reduction in pressure to intermediate levels, as well as after reduction to near normal. Headache was the symptom most commonly improved. The most dramatic improvement noted was in the signs and symptoms of hypertensive encephalopathy. These improved in five patients with malignant hypertension within a few days after lowering of the blood pressure, and remained so as long as the blood pressure was maintained at reduced levels, over a period of one to eight months. One other patient showed no improvement, and one became worse following reduction in the blood pressure to near normal. One patient who had had a subarachnoid hemorrhage improved rapidly following reduction in blood pressure. Exertional dyspnea and orthopnea diminished in several patients, and left ventricular enlargement, palpitation, weakness, giddy spells, and recurrent epistaxes diminished in a few. Retinal hemorrhages, exudates and papilledema improved in approximately half the patients in whom these changes were present, but vision improved in a smaller number. In two patients with malignant hypertension and severe retinopathy there was transient loss of vision following reduction in the blood pressure to normal, but vision returned when the blood pressure rose to intermediate levels.

Effect on the Electrocardiogram. Of 30 patients studied, 22 had abnormal electrocardiograms (19 left ventricular "strain" pattern, two nonspecific T-wave abnormalities, and one left bundle branch block), five had borderline records (left axis deviation and minor T-wave changes), and three had normal records. None of the patients had symptoms or electrocardiographic changes suggestive of coronary insufficiency, as this was regarded as a contraindication to drug administration. Following reduction in blood pressure by hexamethonium or hexamethonium plus hydrazinophthalazine there was moderate improvement in the electrocardiograms of two patients, consisting of disappearance of left ventricular "strain" pattern in one and replacement of left bundle branch block by left ventricular strain in the other, minor improvement in seven, consisting of changes in the

TABLE 1.—*Effect of Reduction of Blood Pressure on Signs and Symptoms Attributable to Hypertension*

	Number of Patients			
	Oral Hexamethonium (27 Patients)		Oral Hexamethonium plus Hydrazinophthalazine (16 Patients)	
	Improved	Not Improved	Improved	Not Improved
Headache	7	5	10	2
Giddy spells	1		4	
Epistaxes			1	
Hypertensive encephalopathy, with drowsiness, clouded sensorium, confusion, nausea, vomiting	1	2 worse	4	
Weakness		4	3	3
Exertional dyspnea	1	3 (1 worse)	7	1
Orthopnea		2 (1 worse)	3	1
Paroxysmal nocturnal dyspnea		2 (1 worse)	4	1
Recurring pulmonary edema	1	1	3	1
Retinal hemorrhages and exudates	2	5	7	2
Papilledema	3	4	2	2
Reduction in vision	1	5	2	2
Palpitation	1	1	3	1
Left ventricular enlargement (x-ray)		12	4	8
Left axis deviation (ECG)		16		13
S-T segment depression and T wave inversion	4	12 (2 worse)	4	9

S-T segments and T waves, no change in 19 patients, and worsening of the electrocardiogram in two patients. There were no significant changes in the QRS axis. None of the abnormal electrocardiograms, and only one of the borderline records, became normal. The two patients who had worsening of the electrocardiogram following reduction in blood pressure were malignant hypertensives, 27 and 44 years of age, whose electrocardiogram had revealed only left axis deviation prior to drug administration. Following gradual reduction in blood pressure from 240/150 to 140/110 by the oral administration of 0.5 to 1 Gm. of hexamethonium a day for four days, both patients experienced slight discomfort over the precordium, and were found to have electrocardiographic changes consisting of increased depression of the S-T segments and sharp inversion of the T waves in the first and second limb and fifth precordial leads. Hexamethonium administration was stopped, following which the blood pressure promptly returned to the original level in the 27 year old patient, and the electrocardiographic changes disappeared in this patient over a period of two weeks. In the other patient (D. M., fig. 11) the blood pressure was unchanged following cessation of hexamethonium, and the electrocardiographic changes became more marked. On the fifth day after cessation of drug there was a further fall in blood pressure, and the patient died after futile attempts to raise the blood pressure by means of shock position and intravenous infusion of saline, glucose, and norepinephrine. Except for this evidence of coronary insufficiency in one patient, and of probable myocardial infarction in another, the electrocardiographic changes observed in the patients with malignant hypertension were similar to those in the patients with benign hypertension. The minor improvement that occurred in some patients could not be correlated with the precise degree or duration of reduction in blood pressure, with the age of the patient, or with the known duration of hypertension. The addition of hydrazinophthalazine did not have any definite influence on the effect of hexamethonium on the electrocardiogram, except to increase the cardiac rate in some patients.

In two patients, one of whom had benign and one malignant hypertension, reduction of the blood pressure by oral hydrazinophthalazine alone to near normotensive levels resulted in nausea and substernal discomfort, deep cove-shaped inversion of the T waves in the second and third limb and fifth precordial leads in one patient, and depression of the S-T segments in the first and second limb and fifth precordial leads in the other patient. These changes, which are compatible with myocardial ischemia or infarction in the former patient, and with coronary insufficiency in the latter, progressed in spite of cessation of drug administration and prompt return of the blood pressure to the original elevated level. The electrocardiogram gradually returned to its original form over a period of two weeks, except for persistence of deep inversion of the T wave in the fifth precordial lead.

Effect on Renal Function: In Patients with Benign Hypertension. These had normal blood nonprotein nitrogen concentration and normal or slightly depressed phenolsulfonphthalein excretion prior to drug administration. There was no significant change in these determinations when the blood pressure was lowered.

In Patients with Malignant Hypertension. Of the 10 who received hexamethonium, one (R. C., fig. 11) had normal excretion of phenolsulfonphthalein and normal blood nonprotein nitrogen concentration, while the remainder had slightly to moderately decreased excretion of phenolsulfonphthalein and slightly elevated blood nonprotein nitrogen. In the former patient and in three of the latter the oral administration of hexamethonium resulted in marked elevation of the blood nonprotein nitrogen concentration following reduction in the recumbent blood pressure to or near normotensive levels. The course of three patients is charted in figure 11. In the fourth patient the blood nonprotein nitrogen rose from 64 to 140 mg. per 100 cc. following reduction of the recumbent blood pressure to near normal by 0.5 to 1 Gm. of hexamethonium daily by mouth for three days. In spite of the cessation

of hexamethonium administration in each instance, and return of the blood pressure to or near the original elevated levels in three of the four patients, nitrogen retention progressed and all died in uremia. Postmortem examination performed in two patients showed severe intrarenal arteriosclerosis, scattered necrotic intraglomerular arterioles, and filling of the renal tubules with acellular material. Of the six other patients four had slight to moderate reduction in recumbent pressure during oral hexamethonium administration and two had reduction to near normotensive levels, with no

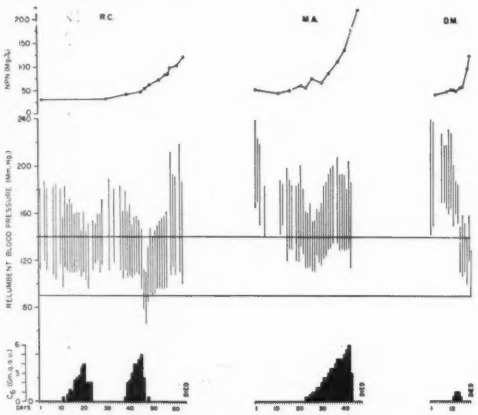

FIG. 11. Development of progressive renal insufficiency in three patients with malignant hypertension following reduction in blood pressure by oral hexamethonium.

alteration in blood nonprotein nitrogen concentration.

The oral administration to six patients of short courses of hexamethonium and of hydrazinophthalazine followed by prolonged courses of the two drugs administered together resulted in slight elevation of blood nonprotein nitrogen during hexamethonium in one patient and during combined drug administration in another, and slight lowering of phenolsulfonphthalein excretion during combined drug administration in two patients. In spite of the greater and more prolonged lowering of blood pressure during combined drug administration than during hexamethonium alone none of the patients developed progressive nitrogen retention during the former.

In no patient did the administration of hexamethonium, hydrazinophthalazine, or both result in any improvement in renal function, as reflected by the concentration of blood nonprotein nitrogen and by the phenolsulfonphthalein excretion.

Patients with Chronic Glomerulonephritis. In two patients with marked renal insufficiency reduction of blood pressure to normotensive levels for relatively brief periods by hexamethonium resulted in only slight transient elevation of nonprotein nitrogen and reduction in phenolsulfonphthalein excretion.

Occurrence of Hemodilution Following Reduction in Blood Pressure by Hexamethonium, Hydrazinophthalazine, or Both. In four patients there was moderate reduction in the hematocrit and red blood count during hexamethonium administration, and in three patients during combined hexamethonium and hydrazinophthalazine. The average hematocrit of these patients was 42 per cent prior to, and 32 per cent after 5 to 12 days of drug administration. In one patient the hematocrit fell during each of two courses of hexamethonium. All the patients had reduction in the recumbent blood pressure to normotensive or intermediate levels, and postural hypotension, during the period of drug administration. Five of the eight patients had malignant hypertension, with some reduction in renal function, but with little or no elevation in the concentration of blood nonprotein nitrogen. In only one patient did the latter increase during drug administration, and this occurred only during the second of two courses. In two patients less marked reduction in the hematocrit and red blood count occurred during 10 days of hydrazinophthalazine administration, the hematocrit falling from 46 per cent to 40 per cent.

Determination of serum protein concentration was performed in only two patients. In both of these, reduction in the concentration of total protein, albumin, and globulin, and in the activity of serum cholinesterase, occurred coincident with and proportionate to the reduction in the hematocrit. In two other patients extracellular fluid volume was determined from the volume of distribution of inulin,[16] and was found to be increased from 11 and 15 liters to

14 and 18 liters, coincident with the reduction in the hematocrit. In spite of the occurrence of hemodilution, and presumably of increased plasma volume as well as of increased extracellular fluid volume, mild pretibial edema was observed in only three patients, and none developed frank signs of cardiac failure. The daily intake of sodium chloride was 1 to 4 (average 2.9) Gm., and was the same during as prior to drug administration. In five patients there was a slight increase in the serum sodium concentration during drug administration, from an average of 134 mEq. per liter to 140 mEq. per liter, but in the other three patients there was no change. There was no alteration in the red blood cell indexes, and no evidence of increased hemolysis. Smears of the bone marrow of two patients were normal.

Continued administration of hexamethonium did not result in further reduction in the hematocrit; in some instances, the hematocrit returned to the original level as the blood pressure rose with the development of tolerance to the drug. Cessation of hexamethonium resulted in rapid return of blood pressure and hematocrit to their original levels. None of the patients who developed rapid tolerance to the drugs, and whose blood pressure did not fall during administration of as much as 9 Gm. of hexamethonium a day, and 800 mg. of hydrazinophthalazine a day, had any reduction in the hematocrit, in the concentration of serum albumin or globulin, or in the activity of serum or red blood cell cholinesterase.

Other Effects of Hexamethonium (Table 2)

The intravenous or oral administration of hexamethonium or pentamethonium resulted in other evidences of autonomic blocking action, in addition to reduction in the recumbent blood pressure and postural hypotension. In most patients there was initially mild dryness of the mouth, slight blurring of vision, constipation, and increased temperature of the extremities, sometimes associated with chilly sensations. Some patients also had slight pupillary dilation, gastric dilatation, anorexia, transient nausea and vomiting, a bitter taste in the mouth, and urinary hesitancy and retention. These effects were rarely severe enough to require any therapeutic measures, and they usually diminished coincident with the development of tolerance to the hypotensive effect of the drug. The constipation could usually be alleviated by laxatives and enemas. Rarely, gastric dilatation, abdominal distention, or urinary symptoms required treatment. These effects could be alleviated by the oral administration of 5 to 10 mg. of urecholine, or by the intramuscular administration of 1 mg. of Neostigmine or of 2 mg. of di-isopropyl fluorophosphate (DFP),[17] followed by 0.5 to 1 mg. of Neostigmine and 10 to 20 units of pitressin. Three patients complained of diminished potentia during the first few weeks of oral hexamethonium administration. Eight patients complained of drowsiness, lethargy, and subjective weakness. These symptoms were mild in all but one patient whose daily intake of hexamethonium

TABLE 2.—*Side Effects of Oral Hexamethonium in 30 Hypertensive Patients*

Effects Attributable to Ganglionic Blockade	Number of Patients
Constipation	12
Abdominal distention	7
Anorexia and nausea	6
Eructation and bitter taste	2
Gastric dilation	1
Vomiting	5
Dry mouth and throat	7
Blurred near vision	7
Dilated pupils	5
Urinary hesitancy	2
Urinary retention	2
Decreased potentia	3
Increased warmth of extremities	4
with subjective warmth	1
with subjective chilliness	2
Effects which May be Due to Central Action	
Drowsiness, lethargy, weakness	8
Paresthesias of mouth, tongue, and extremities	1
Other Effects	
Diarrhea	2*
Reduction in hematocrit	6*

* Two patients were also receiving hydrazinophthalazine.

could not be increased above 3 Gm. a day without the occurrence of moderately severe drowsiness. The drowsiness and lethargy would appear to be referable to a direct effect of methonium on the central nervous system, since these symptoms occurred in some patients following little or no reduction in blood pressure. Subjective weakness occurred concomitant with these symptoms in some patients, but also occurred in their absence following reduction in the blood pressure.

TABLE 3.—*Side Effects of Oral Hydrazinophthalazine in 24 Hypertensive Patients*

	Number of Patients
Headache	7
Pain in back of neck, shoulders, arms	3
Rhinitis, conjunctivitis, lacrimation, photophobia, periorbital edema	4
Hiccups	2
Giddiness in absence of fall in blood pressure	2
Substernal discomfort in absence of fall in blood pressure	2
Subjective warmth	1
Pain in flanks	2
Nausea	2
Tenesmus	1
Diarrhea	2
Weakness	1
Fever	1
Reduction in hematocrit	2

Other Effects of Hydrazinophthalazine (Table 3)

Seven patients developed severe headache and four conjunctivitis, lacrimation, periorbital edema, and coryza. In two patients, one of whom was also receiving hexamethonium, this was associated with severe and protracted hiccups, and in one of these with fever. These effects subsided promptly following discontinuation of the drug. In one patient they did not recur when hydrazinophthalazine was resumed. Other effects are recorded in table 3.

The headache, conjunctivitis, and coryza that may occur during hydrazinophthalazine administration have been ascribed by some to histamine released as a result of the purported antihistaminase activity of hydrazinophthalazine.[11] However, measurement of the daily urinary excretion of acetyl histamine,[18] and of the local wheal and flare produced by graded dilutions of intradermal histamine, revealed no change during drug administration.

Discussion

The oral or intravenous administration of hexamethonium or pentamethonium produced an initial moderate reduction in blood pressure in a majority of hypertensive patients, but continued oral administration resulted in diminished response to either drug. Moderate reduction in recumbent blood pressure by the oral administration of these compounds could be achieved for more than a few days in only a few patients. The initial response to the drugs, administered orally or parenterally, was greatest in those patients (mainly those with malignant hypertension) who had either marked encephalopathy or reduced concentration of sodium in the serum. The cause of the increased reactivity to methonium observed in these patients is not known, although, in the latter patients, associated reduction in plasma volume may have played a part.

The effects of methonium salts could largely be interpreted in terms of the effects of inhibition of ganglionic conduction, including reduction of sympathetic vasoconstrictor tone and partial inhibition of reflexes mediated through the sympathetic and parasympathetic nervous systems. The inhibitory effect of methonium appeared to be more notable on whichever division of autonomic activity is normally greater; for example, parasympathetic in the case of the smooth muscle of the iris, gastrointestinal tract, and bladder, and sympathetic in the case of smooth muscle of the peripheral vascular tree. However, the hypotensive effects of methonium were not always entirely explicable in terms of reduction in sympathetic vasoconstrictor tone alone. Although sympathetic vasoconstrictor tone is believed to make a greater contribution to the elevation of the blood pressure of patients with benign hypertension than of those with malignant hypertension, as reflected by the response to sodium amytal induced sleep, it

was the latter patients who had the more marked initial response to methonium.

After several days of methonium administration tolerance usually developed not only to the effect of the drug on the blood pressure, both recumbent and erect, but also to the other effects attributable to the inhibition of autonomic reflexes, and to the central effects. The mechanism of this tolerance is not known. The observation of hemodilution and of increased extracellular volume following the initial reduction in blood pressure suggests that this reduction may have resulted in increased retention of sodium. Such retention might result in a decrease in the hypotensive effect of methonium. However, while rigid restriction of sodium chloride intake usually delayed the development of tolerance, it did not prevent it, and rapid development of tolerance was observed even in patients whose sodium chloride intake was very restricted, and it was observed in the absence of hemodilution. Therefore it seems likely that other factors are more important in the development of tolerance. The suggestion has been made that decreased absorption of methonium from the intestine may play a part,[7] but this could not explain the development of tolerance to parenterally administered drug. The increased hypotensive response to methonium that occurred following the onset of hypertensive encephalopathy or of cerebral vascular accident indicates that the central nervous system may play an important role in influencing reactivity to methonium.

Hydrazinophthalazine produced a slight to moderate reduction in blood pressure in about half the patients who were studied, and, when this drug was administered concurrently with hexamethonium, the reduction in pressure was greater than following either drug alone and tolerance appeared to develop more slowly. These observations are in conformance with those of Fries[10] and Schroeder.[11] In most patients the effect of the two drugs on the blood pressure appeared to be approximately additive. Following comparable reduction in recumbent blood pressure there was less marked postural hypotension during combined drug administration than during hexamethonium alone, and similar degrees of postural hypotension appeared to be somewhat better tolerated. These effects of combined drug administration may be due to the effect of hydrazinophthalazine in reducing hexamethonium requirement and in increasing cardiac output by increasing cardiac rate, and, as has been demonstrated following intravenous administration,[19] by increasing stroke volume. The latter effect may be particularly important since moderate or marked reduction in recumbent pressure by (intravenous) methonium is accompanied by a reduction in stroke volume and cardiac output,[20] probably owing to decreased venous return to the heart resulting from pooling of blood in the peripheral circulation. The reduction in stroke volume and cardiac output becomes even more marked when the blood pressure falls further on standing.

Even during combined drug administration, it was seldom possible to lower the recumbent blood pressure to consistently normal levels without producing intermittent severe postural hypotension. However, moderate reduction in recumbent pressure, to levels intermediate between the original and normotensive, could usually be achieved with only occasional marked postural hypotension. This moderate reduction in recumbent pressure was sufficient to produce improvement in many of the signs and symptoms attributable to hypertension, particularly those attributable to hypertensive encephalopathy, and to a lesser degree, retinopathy and left ventricular strain.

Following reduction in pressure to or near normal by oral hexamethonium a marked decrease in renal function occurred in four patients, electrocardiographic changes compatible with coronary insufficiency occurred in two, transient loss of vision in two, and increased encephalopathy in one. All of these patients had malignant hypertension. Since untoward effects of reduction in blood pressure were noted mainly in the patients with malignant hypertension, it would appear that the danger of reduced blood flow to the kidneys, heart, retina, and brain is greater in these patients, who probably have a greater degree of fixed vascular change, than in patients with

benign hypertension. The progression of renal insufficiency to uremia in spite of discontinuation of drug administration and return of the elevated blood pressure indicates that transient reduction in blood pressure by hexamethonium may lead to irreversible renal changes in patients with malignant hypertension. In almost all the patients who were studied, the occurrence of syncope during postural hypotension indicated transient reduction in cerebral blood flow at this time.

Following moderate reduction in blood pressure by hydrazinophthalazine, symptoms and electrocardiographic changes compatible with coronary insufficiency occurred in one patient with benign hypertension and in one with malignant hypertension. None of the patients who were studied developed more than mild and transient evidence of reduction in renal function following reduction in blood pressure by hydrazinophthalazine, or by this drug plus hexamethonium. Intravenous hydrazinophthalazine has been found to increase renal blood flow in many hypertensive patients.[19] Oral hydrazinophthalazine did not significantly increase renal blood flow, but it did appear to lessen the effect of reduction in blood pressure by intravenous hexamethonium on renal blood flow, and, to a lesser extent, on glomerular filtration rate.[20] While observations on the clinical effects of these compounds in a larger number of patients will be necessary to confirm the apparent action of hydrazinophthalazine in reducing the incidence of renal insufficiency during hexamethonium administration, the available data do suggest that the concurrent administration of the two drugs not only enables greater and more prolonged reduction of blood pressure than does hexamethonium alone, but may also result in less untoward effects following comparable reduction in blood pressure. They also indicate that it may be desirable to begin the administration of hydrazinophthalazine before that of hexamethonium.

The goal in therapy of hypertensive patients is of course to lower the blood pressure without seriously reducing blood flow to the vital organs. This necessitates careful adjustment of drug dose to prevent rapid or excessive fall in blood pressure, both recumbent and erect, especially in patients with reduced serum sodium concentration or marked encephalopathy. In patients with renal insufficiency or malignant hypertension frequent determinations of the concentration of nonprotein nitrogen in the blood must be carried out, particularly during the initial period of blood pressure reduction. The presence of evidence of coronary insufficiency or of recent cerebral thrombosis has been considered to be a contraindication to attempted reduction in blood pressure. In view of the hazards that are involved, and the lack of information concerning the long term effects on the course of the disease, it would appear reasonable at this time not to administer these drugs routinely to patients with mild or asymptomatic hypertension, but to reserve them for patients in whom there are strong indications for lowering the blood pressure, such as hypertensive crises and encephalopathy, severe retinopathy, left heart failure, and subarachnoid hemorrhage. It would appear to be safer to aim for a reduction in blood pressure to intermediate than to normal levels, particularly in patients with malignant hypertension and in those who are ambulatory. It seems likely that other autonomic blocking drugs, or combinations of drugs, will be introduced which will prove to be even more satisfactory agents for reduction of blood pressure without impairment of blood flow.

Summary

1. Hexamethonium and pentamethonium produced comparable reduction in the blood pressure of hypertensive patients, following intravenous or oral administration. The reduction in pressure was greatest in the patients with malignant hypertension who had low serum concentration of sodium or severe encephalopathy. The response to methonium was increased by sodium depletion and by sympathectomy, and decreased by sodium restitution.

2. The repeated oral administration of hexamethonium or hydrazinophthalazine resulted in a reduction in the blood pressure of most hypertensive patients to levels intermediate between the original and normo-

tensive levels, and a slight reduction in the remainder. The development of tolerance necessitated increasing doses. Concurrent administration of the two drugs resulted in an additive effect on the blood pressure of most patients, with slower development of tolerance and less marked postural hypotension than following hexamethonium alone. It was possible to maintain the blood pressure of most patients with benign or malignant hypertension at intermediate levels for a period of several months. This resulted in improvement in many patients in signs and symptoms attributable to encephalopathy, and, to a lesser degree, to left ventricular decompensation and retinopathy. Improvement in the electrocardiogram occurred in a minority of patients.

3. Harmful effects of reduction in blood pressure occurred mainly in patients with malignant hypertension, and consisted of evidence of myocardial ischemia in four patients, of retinal ischemia in two, and renal insufficiency which progressed to terminal uremia in four. The latter occurred following hexamethonium administration, but was not observed in a smaller group of patients following concurrent administration of hexamethonium and hydrazinophthalazine. Some patients developed reduction in the hematocrit, which was attributable to hemodilution, following reduction in the blood pressure. An increase in extracellular fluid volume was measured in two patients.

4. The side effects of hexamethonium were minor, consisting of other evidences of autonomic blocking action, and, in a few patients, drowsiness and weakness. The side effects of hydrazinophthalazine consisted of headache, conjunctivitis, coryza, and, in a few patients, hiccups or fever.

Acknowledgments

The authors are indebted to Drs. A. McGehee Harvey and E. Cowles Andrus for their support and encouragement. Dr. Donald A. Searle of Burroughs Wellcome Company, Tuckahoe, New York, provided the hexamethonium (Hexameton) that was employed, and Dr. Jock L. Graeme of Ciba Pharmaceutical Company, Summit, New Jersey, provided the hydrazinophthalazine (Apresoline).

Sumario Español

Hexamethonium y pentamethonium produjeron una reducción mayor en la presión arterial en pacientes con hipertensión maligna que tenían una concentración del suero sódico baja o una encefalopatía que en aquellos con hipertensión benigna. Administración concurrente de hydrazinophthalazine resultó en un efecto aditivo en la presión arterial de la mayoría de los pacientes, con menor desarrollo de tolerancia y menor hipotensión postural. En muchos de los pacientes hubo signos y síntomas de mejoría atributables a la hipertensión. Efectos nocivos de la reducción en presión arterial ocurrieron principalmente en los pacientes con hipertensión maligna y consistieron en insuficiencia renal y evidencia de isquemia del miocardio y retinal.

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Effect of Dibenzyline on Skin Temperature, Peripheral Blood Flow, and Vasomotor Responses in Normal Patients and Patients with Increased Vasoconstrictor Tone

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Dibenzyline is an orally effective, moderately potent, long acting, adrenergic blocking agent. The drug is capable of at least partially preventing the vasoconstrictor responses to cold and to injected Neosynephrine. Blood flow and temperature responses to this agent do not always parallel results obtained following surgical sympathectomy, but the degree of effect appears to be sufficient to produce a clinical response. Side effects and the development of "tolerance" may limit the use of Dibenzyline in clinical medicine.

SEVERAL reports have appeared during the past year confirming the observation that Dibenzyline (SKF 688A) is a specific sympathetic blocking agent.[1-3] It is similar in action to Dibenamine, but is more potent, less toxic and is orally effective. The clinical usefulness of the drug has not been completely established. There is evidence to support its usefulness in the treatment of some peripheral diseases,[4, 5] a limited group of hypertensive patients,[6] and in patients with pheochromocytoma.[7] Some observers have obtained a blockade of the pressor response to cold or intravenous Neosynephrine with oral Dibenzyline in both normotensive and hypertensive individuals.[3, 4, 6] Others have failed to note a significant change in blood flow or vasomotor responses after oral medication.[8] Woodward, Hoobler, and Nickerson, however, obtained marked increases in foot blood flow following intravenous administration of Dibenzyline at room temperatures.[9]

It is the purpose of this report to summarize our findings in a group of normal patients and patients with normal blood pressure but evidence of increased vasoconstrictor tone who were given single or multiple blocking doses of oral, intravenous, or intra-arterial Dibenzyline.* Subcutaneous or intramuscular administration was not used because of the possibility of producing local tissue necrosis. Results of long-term administration and comparative studies with Priscoline, penta-, and hexamethonium will be published elsewhere.[5, 10]

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Materials and Methods

Fifty-five normotensive patients were studied. Forty of these had evidence of "sympatheticotonia" manifested by: (1) a marked fall in skin temperature following exposure to cold for 20 minutes, (2) cold, clammy extremities at ordinary room temperature, and (3) acrocyanosis or Raynaud's phenomena. Fifteen patients had normal peripheral vascular systems. Twelve had had unilateral sympathectomies for "abnormal vasospasm" or causalgic states.

Thirty-six patients received 60 to 200 mg. of oral Dibenzyline in single or divided doses, eight were given 0.7 to 1.0 mg. per kilogram in a 200 cc. infusion over a 35 to 40 minute period, 10 were given 1 mg. per kilogram diluted in 10 cc. of saline solution intravenously within a four to seven minute period, and six received intra-arterial Dibenzyline (35 to 80 mg.) in the femoral artery within a three to four minute period. Some patients were given both oral and parenteral medication.

Observations were carried out in a constant temperature room with the patients lightly clothed.

* Supplied by Smith, Kline and French Laboratories, Philadelphia, Pa.

series of determinations were made in a warm environment, 25 to 27 C. (77 to 82 F.); at usual room temperatures, 22 to 25 C. (71.5 to 77 F.); at cool environments, 19 to 22 C. (66 to 71.5 F.); and in a cold room, 10 to 19 C. (50 to 66 F.).

Skin temperatures in all patients were determined with the Leeds Northrup Potentiometer. The venous occlusion plethysmograph[11] was used to measure digital blood flow in 19 subjects. Blood pressure and blood flow response following 1.0 mg. of intravenous Neosynephrine and immersion of the hand in water at 4 C. (39 F.) were determined before and after administration of Dibenzyline in 12 patients in order to judge the degree of sympathetic blockade.

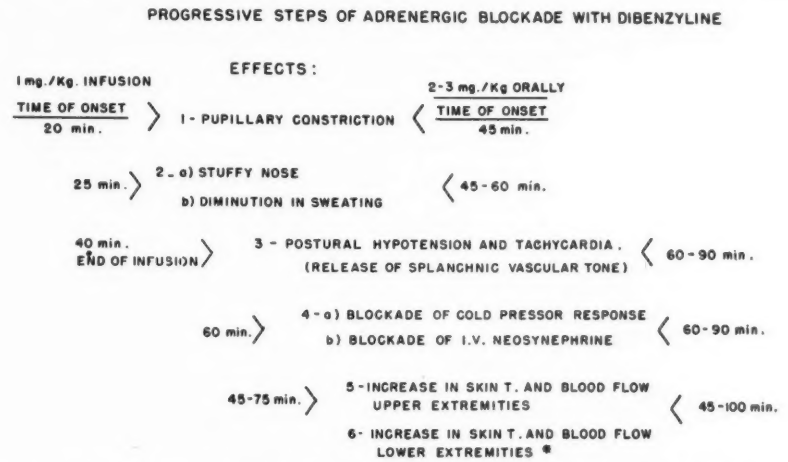


FIG. 1. Outline of time of onset of effect and results of adrenergic blockade with Dibenzyline.

* Not constant with above doses.

The cobalt chloride test for determining the presence of sweating was carried out for the same purpose in eight patients. Blood pressure and pulse in the recumbent, sitting, and standing positions were also recorded at frequent intervals following the administration of the drug.

RESULTS

Time of Onset of Action. Following intravenous injection of 50 to 75 mg. of Dibenzyline over a four to seven minute period, the first evidence of effect was usually noted within 5 to 15 minutes. A significant adrenergic blockade, however, was not established for 30 to 40 minutes. Intra-arterial administration did not produce a more rapid effect. Onset of action following oral administration or an intravenous infusion given over a 30 to 45 minute period varied a great deal from person to person and even in the same individual after repeated doses. Duration of action following a single dose varied between 5 and 36 hours.

Establishment of an Adrenergic Blockade. Evidence of an adrenergic blockade (fig. 1) occurred in the following sequence:

(1) Partial to complete inhibition of pupillary dilatation; pupils could not be dilated with Paredrine. Homatropine produced satisfactory dilatation.

(2a) Nasal congestion, indicating blockade of sympathetic vasoconstrictor fibers to the nasal blood vessels; local application of Neosynephrine did not relieve the congestion.

(2b) Definite diminution of sweating at average room temperature. Complete inhibition of sweating as determined by the use of the cobalt chloride "hot box" technic did not occur.

(3) Postural hypotension and tachycardia. The fall in blood pressure in the upright position was only partially prevented by the use of ace bandages or tourniquets applied to the thighs. It was usually decreased considerably by the application of a tight abdominal binder. These findings were interpreted to indicate that at least part of the postural blood pressure changes were secondary to a release of splanchnic vascular tone in addition to some pooling of blood in the lower extremities. A significant fall in recumbent blood pressure did not occur.

(4) A partial inhibition of the blood pressure rise after immersion of the hand in water at 4 C. (39 F.) for one minute in the 12 patients tested. Complete blockade was noted in only two. A partial or complete inhibition of the blood pressure rise following 1.0 mg. of intravenous Neosynephrine occurred in 10 patients. In two, a transient fall in pressure occurred after Dibenzyline (fig. 2). As recorded plethysmographically, the pulse volume decrease,

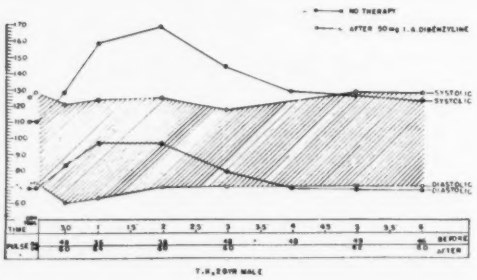


FIG. 2. Blood pressure response to 1.0 mg. Neosynephrine, intravenously, before and after Dibenzyline. A transient fall in both systolic and diastolic pressure is noted after medication.

usually noted after the above procedures, was completely eliminated in only two cases.

Effect on Skin Temperature and Blood Flow

The response obtained varied greatly. It depended upon the temperature of the room at the time Dibenzyline was administered, whether the upper or lower extremities were studied, and upon the degree of vasoconstriction present when the drug was given.

Results at Moderate Room Temperatures (22 to 25 C.). At ordinary room temperatures (22 to 25 C.) (71.5 to 77 F.) and at temperatures above 25 C., a rise in skin temperature of from 4 to 7 C. (7 to 12 F.) and/or blood flow (three to eight times control levels) uniformly occurred in the upper extremities. Sixty to 180 mg. orally or 1 mg. per kilogram intravenously produced a gradual increase in pulse volume, blood flow, and skin temperature which was greatest one and one-half hours after the administration of the drug. In four patients who had had unilateral dorsal sympathectomies for causalgic states or "vasospastic" phenomena, Dibenzyline produced changes in the normal contralateral extremity which compared favorably with those on the denervated side (fig. 3). In the doses administered, abnormal vasoconstriction was abolished.

Skin temperature determinations were not closely correlated with blood flow results at high skin temperatures; a rise from 31 to 32 C (88 to 89.5 F.), although seemingly slight

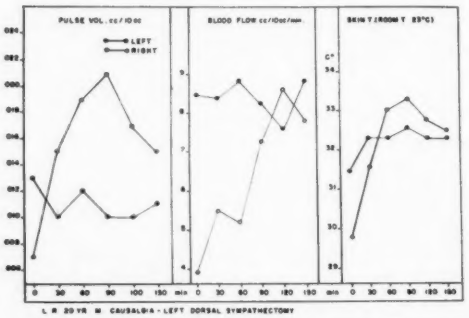
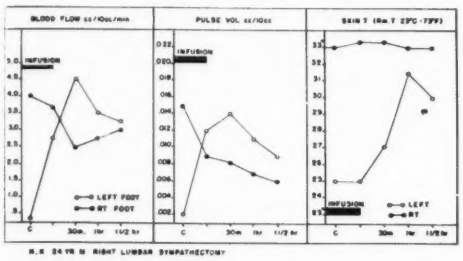


FIG. 3. Effects of 120 mg. of oral Dibenzyline on blood flow in a normal upper extremity as compared with the contralateral sympathectomized limb. Room temperature 23 C. (73 F.).

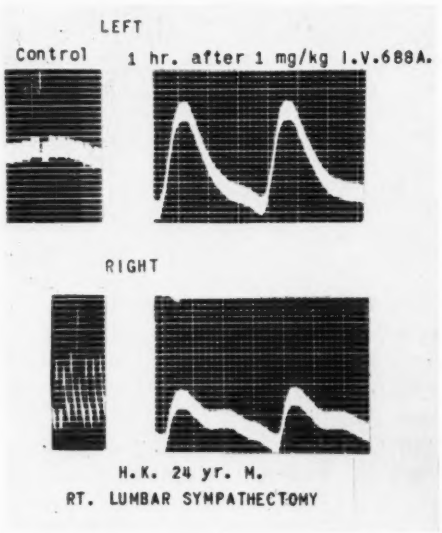
actually represented a 50 to 100 per cent increase in blood flow in some cases. Skin temperature changes from 22 to 30 C. (71.5 to 86 F.) usually paralleled alterations in blood flow. There was a delay in skin temperature response as compared to blood flow response.

Oral or intravenous Dibenzyline produced an increase in skin temperature (4 to 8 C.) (7 to 14 F.) and/or blood flow (two to six times resting level) in the lower extremities at a room temperature of 22 to 25 C. in all but four patients. The changes in the intact limb equalled those produced by lumbar sympathectomy in 7 of the 10 patients who had had unilateral denervation prior to the study (figs. 4*a* and 4*b*). In the other three, increases were less than in the sympathectomized limb. In patients with a high degree of sympathetic overactivity, as evidenced by the presence of hyperhidrosis and cold and cyanotic extremities, marked vasodilatation was not obtained in the lower extremities with the doses used. In general, results obtained with intravenous Dibenzyline were more constant than with oral medication.

Thirty-five milligrams of intra-arterial Di-
benzyline produced no appreciable change in
skin temperature in the injected extremity.



a



b

FIG. 4(*a*). Effect of intravenous Dibenzyline (1 mg. per kilogram) on blood flow pulse volume and skin temperature in a normal as compared with a denervated lower extremity. Skin temperature in the denervated limb does not reflect the decrease in blood flow or pulse volume that results from "redistribution" of blood.

(*b*). Pulse volume tracing before and after Dibenzyline (688A) in same patient as figure 4*a*. Slow speed used during control tracing. Pulse volume greater in intact limb after Dibenzyline than in denervated limb.

Fifty milligrams or more produced a rise in skin temperature from 5 to 9 C. in five of the six patients tested. In one patient with a unilateral sympathectomy, temperatures on the contralateral injected limb rose to equal those of the denervated limb. Evidence of marked sympathetic overactivity was present in the one patient who did not obtain a rise of more than 3 C. (5 F.). In only one instance was there evidence that the drug was "trapped" in the injected extremity. In the other patients, systemic effects occurred and there was no evidence to suggest a more marked effect on flow in the injected limb following intra-arterial injection.

Results at Cool Temperatures (19 to 22 C.). At room temperatures of 19 to 22 C., a rise in skin temperature (6 to 12 C.) (11 to 21.5 F.) and/or blood flow (three to eight fold increase) in the upper extremities occurred in only 14 of 20 patients who received oral Dibenzyline. A rise in skin temperature and blood flow was noted in six of eight patients who were given the drug intravenously. All of those who did not obtain a satisfactory response were patients who showed evidence of increased vasoconstrictor tone before therapy.

Results in the lower extremities were unpredictable. In four patients with normal extremities, an increase in skin temperature and blood flow occurred. Only one out of eight patients with increased "vasomotor tone" tested at this temperature experienced a significant effect upon blood flow. The other seven obtained poor responses from both oral and intravenous medication.

Changes in peripheral circulation did not occur despite the fact that other effects indicative of at least a partial adrenergic blockade were present, namely, stuffy nose, miosis, postural tachycardia, and blockade of the blood pressure response to cold stimuli.

Results of Cold Room Studies. Thirty-one patients were given 60 to 120 mg. of oral Dibenzyline while at a room temperature of 22 to 25 C. and after 90 minutes were placed in a cold room (12 to 15 C.) for 20 minutes. This procedure was carried out on numerous occasions over a period of five to six weeks in several cases. Six of these patients were considered to have normal extremities. Fourteen had had unilateral dorsal or lumbar sympathectomies and of these, six were considered

to have normal contralateral limbs. Eleven had definite evidence of sympathetic overactivity as manifested by increased sweating, acrocyanosis, Raynaud's phenomena, and an abnormal skin temperature response to a cold environment.

In the six patients with normal extremities, the skin temperature upon exposure to cold averaged 8 C. (14 F.) higher after Dibenzyline therapy than before. In those with unilateral sympathectomies, the degree of "protection"

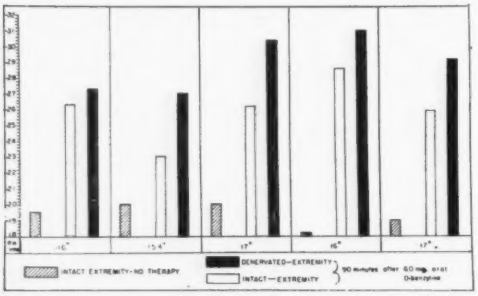


FIG. 5. Comparative effect of Dibenzyline and sympathectomy on skin temperature response to cold (lower extremity). Lower extremity skin temperature response to cold (20 minutes at 15.4 to 17 C.) in five patients before and after unilateral limb denervation by lumbar sympathectomy. Following Dibenzyline, "vasoconstrictor" response is blocked to a considerable degree in the intact normal extremity. Degree of "blockade," however, is not as marked as on denervated side.

against vasoconstriction following exposure to cold environment was considerable in the intact limb. It did not, however, equal the results obtained by sympathetic denervation. Five cases illustrating the effect of Dibenzyline as compared with sympathectomy are shown in figure 5.

The degree of "protection" was usually less in patients with evidence of excessive vasoconstrictor activity, but was significant (over 4 C.) in all but four cases. The effectiveness of Dibenzyline decreased somewhat following repeated studies. It was also noted that the temperature response to cold in the sympathectomized extremities partially returned within six to eight weeks following denervation. Only a slight increase of "vasomotor tone" was noted after that time, several patients having been studied as long as seven years after a sympathectomy.

Ten patients received oral Dibenzyline (100 to 160 mg.) while at a room temperature of 15 C. No effect upon skin temperature in either upper or lower extremities occurred despite the presence of miosis, stuffy nose and postural tachycardia.

Toxicity and Side Effects

The major side effects encountered are listed in table 1. With the exception of palpitations and extreme drowsiness, the side effects were not severe in this group of patients without

TABLE 1.—*Toxicity and Side Effects of Dibenzyline (SKF 688A) in Normotensive Patients*

1. Dryness of mouth and stuffy nose	49 pts.
2. Transient drowsiness, weakness, fatigue	27 pts.
3. Transient dizziness and palpitations	20 pts.
4. Decrease in amount of seminal fluid	14 pts.
5. Nausea and vomiting	3 pts.
6. Transient restlessness and tenseness	1 pt.
Total number of patients studied	55

evidence of cardiac or pulmonary disease. (In a patient with primary pulmonary arteriosclerosis who was not included in this series, sudden death, following respiratory and cardiac arrest, occurred approximately eight minutes after he received 40 mg. of Dibenzyline intravenously over a five to seven minute period. The patient was taking quinidine and had received 0.6 Gm. one and one-half hours before Dibenzyline was given.) Following repeated doses of the drug, reactions were usually less marked, but in some patients no relief was noted. Symptoms often lasted as long as 48 to 72 hours after a single large dose.

Patients were usually kept in bed, either flat or semirecumbent, for two to three hours following intravenous administration of Dibenzyline and were cautioned regarding rapid postural changes for the next 24 to 48 hours. Those who received smaller oral blocking doses only occasionally experienced difficulty and usually remained ambulatory. No actual syncope occurred in normotensive patients although several experienced episodes of

"faintness" (an "all gone" feeling) and had to lie down to avoid fainting.

Discussion

We have been able to confirm the observations that Dibenzyline is a moderately potent adrenergic blocking agent, effective parenterally or orally.[3, 6] The drug should be given slowly, preferably in an infusion over a 30 to 45 minute period when used intravenously. It does not appear to be as toxic as the parent substance, Dibenamine.[12] Its administration, however, in patients with cardiac or pulmonary disease, or patients receiving other potent drugs such as Quinidine should be carried out with great caution. If the drug is used for these patients the oral route is to be preferred. Intra-arterial injection, although effective, does not appear to produce a "local" effect without systemic manifestations of action and consequently presents no advantages over other methods of administration.

Onset of action following intravenous or intra-arterial injection varies, but a satisfactory blockade is usually produced in approximately 30 to 60 minutes after the injection. In an occasional case, a good blockade is present within 10 to 20 minutes. This is in contrast to the action of other blocking agents—the methonium derivatives and Priscoline—where parenteral administration produces an almost immediate response. Orally, adrenergic blockade is not established for 60 to 90 minutes. It has been suggested that an "equilibrium" phase between Dibenamine-like substances and a "receptor" substance exists before the actual chemical blockade occurs.[13] This would serve to explain the delay in onset of action of Dibenzyline. The duration of action following a large blocking dose varies between 3 and 30 hours. Whether the drug is stored in fat depots and slowly released[14] or remains in a firm chemical bond with a "receptor" substance has not been determined.

The absorption of Dibenzyline orally seems to be complete in some patients. These achieve a satisfactory blockade on 1 mg. per kilogram regardless of the route of administration; others require 2 to 2.5 mg. per kilogram orally to produce an equivalent effect. In an occasional patient, evidence of drug action is not observed. These factors of absorption may account for the varying results reported when the oral route of administration is used.[9]

In the doses employed, Dibenzyline appears to produce a blockade of successive vascular beds. Apparently the areas with the least amount of "sympathetic tone" are affected first. In most instances nasal vasoconstriction and pupillary dilatation are inhibited before other effects are noted. Indirect evidence of a release of splanchnic vascular tone (postural hypotension relieved by an abdominal binder) occurs at approximately the same time as the blockade of the blood pressure response to cold stimuli or neosynephrine.

In contrast to the above effects, the drug does not uniformly inhibit the sympathetic nervous system effect on peripheral blood vessels as evidenced by skin temperature and blood flow response. Increase in skin temperature and/or blood flow does not uniformly occur in the lower extremities, especially in patients with an abnormally high degree of vasoconstrictor tone despite the demonstration of an adrenergic blockade in other areas. Upper extremity responses are more constant. This difference in upper and lower extremity response is also seen when other *peripheral* blocking agents such as C.C.K.179 (Hydergine)* or Priscoline are tested.[10] Other observers have noted this difference in response.[15] When *ganglionic* blocking agents, pentamethonium† or hexamethonium‡ or tetraethylammonium chloride are given, however, the most uniform response is noted in the lower extremities.[10, 15, 16, 17] This might suggest that the site of blockade is the determining factor in these varying responses. It is also possible that the *peripheral* blocking agents in the doses given do not produce a blockade complete enough to overcome the vasoconstrictor tone of the lower extremities. This explanation appears more probable in view of the lack of blood flow response in the patients who received Dibenzyline at room temperatures below 21 C.

* Supplied by Sandoz Pharmaceutical Co., New York, N. Y.

† Supplied by Parke Davis Co., Detroit, Mich.

‡ Supplied by E. R. Squibb, Co., New York, N. Y.

(72 F.), as contrasted to the satisfactory response at room temperatures of 22 to 25 C. At the lower room temperatures a fixed degree of vasoconstrictor tone, which apparently cannot be overcome, is maintained.

When Dibenzyline is given, however, while at moderate room temperatures (22 to 25 C.) and the patient then subjected to a cool or cold environment, a marked vasoconstrictor response is prevented in both the upper and lower extremities. This observation is of great importance in considering the clinical usefulness of the drug. Since the agent is usually administered to patients at ordinary room temperatures, an effect on peripheral blood flow and skin temperature may be expected and a blockade of the pressor and vasoconstrictor response to subsequent cold environments will be obtained.

Its oral effectiveness and long duration of action are also important factors which indicate that Dibenzyline may have a place in the treatment of peripheral vascular disease. The drug, however, especially when given orally, does not appear to be suitable for use in increasing blood flow to an extremity in patients who receive it while in a cool or cold environment. In this regard it is not as effective, at least in the dosages given, as Hexamethonium or surgical nerve blocks which produce more constant results in cool environments.[17]

The degree of "protection" produced by Dibenzyline against cold is not as great as that provided by surgical sympathectomy, but it appears to be sufficient to produce clinical results. A gradual return of the vasoconstrictor ability of the peripheral vessels has been noted during the weeks or months following sympathectomy.[18, 19] This was observed in our patients who were studied after sympathectomy and following repeated doses of Dibenzyline. Evidence of sympathetic denervation or blockade was present in other areas, however, and it was concluded that a vascular adjustment or an increase in "intrinsic vascular tone" had occurred. This may explain the occurrence of so-called "tolerance" to drug effect which occurs on prolonged Dibenzyline therapy. In only a few patients could actual tolerance be demonstrated. In many instances the decreasing effect may represent an "adjustment" similar to that following surgical denervation.

The side effects of this drug are related to its sympathetic blocking action and are occasionally troublesome. The soporific effect of Dibenzyline suggests some central action, perhaps on the hypothalamic or cortical areas.

The "quinidine-like" effect of the drug on heart muscle[14] was not noted in the group of normal patients but should be kept in mind when Dibenzyline is given to patients with cardiac disease.

Summary

1. Dibenzyline appears to be a moderately potent, specific adrenergic blocking agent, effective parenterally (1 mg. per kilogram) and orally (1 to 25 mg. per kilogram). Duration of action is from 3 to 72 hours.

2. Blood flow responses to Dibenzyline are irregular when the drug is given in a cool or cold room, especially if the patient has evidence of increased vasoconstrictor tone.

3. When Dibenzyline is given at room temperatures, an increase in blood flow and skin temperature, and at least a partial blockade of vasomotor responses to cold and intravenous neosynephrine is noted in both upper and lower extremities. The degree of response is not always comparable to results obtained with sympathectomy, especially in the lower extremities, but appears to be adequate for clinical effect.

4. These observations suggest that the drug may be of value in *certain cases* of peripheral vascular disease, acrocyanosis, and hypertension where a sympathetic blockade is indicated. Its oral effectiveness and long duration of action present definite advantages over other available blocking agents. It should be given at room temperatures to obtain maximum effect. Side effects and "adjustment" or "tolerance" to drug effect may limit its use in clinical medicine.

Sumario Español

La Dibencilina es un agente bloqueador adrenérgico oralmente efectivo, moderadamente potente y de acción prolongada. La droga es

capaz de por lo menos parcialmente evitar la repuesta vasoconstrictora al frío y a la neosinefrina inyectada. Los resultados en cuanto a circulación de sangre y la repuesta a la temperatura a esta droga no siempre igualan a los resultados luego de una simpatectomía quirúrgica, pero el grado del efecto aparece ser suficiente para producir repuestas clínicas. Efectos no deseables y el desarrollo de "tolerancia" puede que limiten el uso de la Dibencilina en la medicina clínica.

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A Comparison of Direct and Indirect Blood-Pressure Determinations

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In this study a comparison between direct and indirect methods of obtaining blood pressure has been made. A statistical analysis of the data supports the view that the muffling of sounds, or the fourth phase of Korotkow, bears a closer and more constant relationship to diastolic pressure measured directly. This report, therefore, recommends the acceptance of muffling of the sounds of Korotkow as the measure of diastolic pressure.

IN January 1952, the Ontario Heart Foundation circulated a report of the American Heart Association, "Recommendations for the Determination of Blood pressure" and requested comments and criticism as to whether these recommendations should be accepted for distribution to Ontario physicians. The recommendations of the American Heart Association,[1] contain the following paragraph: "While some difficulties still exist in making absolute comparisons between pressures determined by optical manometers and those revealed by auscultatory criteria, a limited number of such comparisons strongly suggests that, on the average, the cessation of sounds conforms rather better to the intra-arterial diastolic pressure, and that dulling of sounds appears 5 to 10 mm. Hg above this level."

In view of the fact that the above statement would favor a departure from what has been widely accepted clinical practice for many years, it was felt that further observations should be made so that any recommendations made by us would not be just an opinion reply, but based on experimental data. In the first part of this report a statistical analysis of the results of blood-pressure determinations both intra-arterially, and indirectly, on 50 patients, was therefore undertaken, with the further objective of comparing the relative merits of two commercially available recording instruments; one, a so-called "strain gauge" manometer, the other an instrument employing a condenser microphone principle (electromanometer). In the second portion, a study of indirect pressure recordings on 15 young normal individuals under varying physiologic conditions was carried out.

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This work was also supported in part by Grants from Defense Research Board (Canada), The Ontario Heart Foundation, and the N.R.C. (Can.).

PART I

Method

In this study observations were made on one arterial segment, the right brachial in each case, in the following manner: The patient was placed in the recumbent position on a hospital bed which allowed him complete comfort and relaxation. The cuff of a commercial sphygmomanometer was placed around the patient's right arm (which rested on pillows at an oblique angle to his body), as close to the axilla as possible. The arm was then adjusted to a position constant for each patient, 5.0 cm. measured in a vertical direction below the angle of Louis.

After determining by palpation the course of the brachial artery in the antecubital fossa and preparing the skin with iodine and alcohol, generous amounts of 1 per cent Novocaine were used to infiltrate skin, subcutaneous tissues, and arterial wall. When local anesthesia was complete, a clean entry was made into the arterial segment, using a Cournand needle. Corroborative evidence of such an entry was demanded by observing a full free spurt of arterial blood from the needle hub upon withdrawing the small-bore inner needle. In a few instances these requirements were not obtained, and such cases are not included in this series. Provided such evidence was obtained, further insertion, proximally, into the artery was carried out, and connection was made by a glass adapter, and a 3 inch portion of "Tygon" tubing, to the recording system, previously adjusted to the height of the anterior surface of the patient's arm. The recording system was composed of a

strain-gauge manometer and electromanometer connected by a three-way stopcock and suitable lengths of lead tubing to the hub of the intra-arterial needle (figure 1). The manometers used were new, commercially-available models, previously carefully calibrated against mercury manometers and thoroughly warmed and checked for balance before each experiment. The electrical connections of the manometers were led through a control switch box to a cathode-ray screen where the pressure tracings were viewed and photographed. With this arrangement either manometer could be used interchangeably by a simple stopcock maneuver.

Intra-arterial pressures, as determined by the electromanometer, were routinely viewed first on the cathode screen and, if pulse-wave contours were satisfactory, a recording was made immediately.

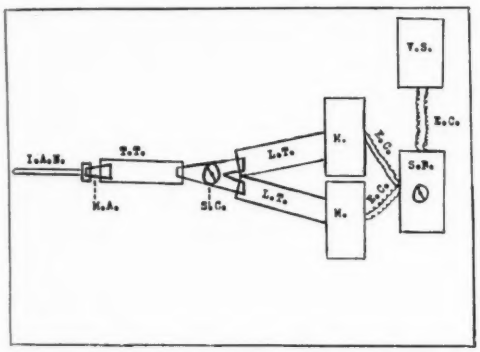

FIG. 1. Diagrammatic representation of recording system. Abbreviations: I.A.N.—intra-arterial needle; M.A.—male adapter; T.T.—"Tygon" tubing; S.C.—three-way stopcock; L.T.—lead tubing; M.—manometer; E.C.—electrical connections; S.B.—switch-box; V.S.—cathode-ray viewing screen.

While the intra-arterial record was being photographed, an indirect measurement of blood pressure in the same arterial segment was made, using the sphygmomanometer cuff already in position. Care was taken in placing the phonendoscope head so that it overlay the portion of the brachial artery distal to the blood-pressure cuff, but just proximal to the point of the indwelling arterial needle. At this point in the procedure, during most of the determinations, the intra-arterial needle was flushed with heparinized saline, a careful check made of tubing and connections, and the procedure repeated in an exactly similar manner, using, however, the strain-gauge manometer. At the end of both readings, and before removal of the intra-arterial needle, a further indirect blood-pressure measurement was recorded. It was realized, however, as experience grew with the technic, that with a single short occlusion of an artery by an external cuff, thrombus formation in the intra-arterial needle did not occur, and that each set of readings, therefore, could follow one another closely without interrupting the recording. Following the pressure determinations, the intra-arterial needle was quickly withdrawn, and firm manual pressure maintained over the site of insertion through a gauze pad, for never less than 10 minutes. A simple sterile dressing was applied over the area, and the patient instructed to use his right arm and hand freely.

As steady a physiologic state as possible in the subjects being investigated was maintained. The patients used in this study were volunteers from the medical wards of the Departments of Veterans' Affairs Westminster and Victoria Hospitals, London, Ontario; nearly all were 70 years of age or over, and proved to be co-operative, relaxed, and philosophical in regard to the investigation. Careful preliminary explanation of the aims and method of study, given in all cases, was of definite value in encouraging the relaxed state during a preliminary 15 to 30 minute period of rest in the recumbent position. Before attempting intra-arterial injection, cuff pressures were quietly taken every five minutes. When a relatively constant blood pressure was evident, the intra-arterial procedures described above were carried out. Another great advantage of elderly male patients is the close proximinity of the brachial artery to the skin in the antecubital fossa, and the consequent relative ease with which painless intra-arterial puncture may be accomplished. Mönckeberg calcification presented no problem whatsoever.

Results

In table 1 the data obtained, using the intra-arterial technic described above with single direct manometric recordings in 47 cases, and double direct recordings in 30 cases, together with the indirect cuff readings, are presented. In this table, blood-pressure readings are indicated in the usual manner, the systolic being placed over the diastolic, and the latter (in the case of indirect readings) being represented by two figures, the first being the pressure in mm. Hg obtained at the onset of muffling of the sounds of Korotkow, and the second representing a similar pressure obtained just at the final disappearance of the sounds. All indirect observations were made by one person, using the same mercury manometer. These pressures are contrasted in the table with the direct manometer recordings, the difference between the two sets of figures being illustrated as positive or negative, depending on their variation up or down from the manom-

TABLE 1.—*Records of Simultaneous Blood Pressure Determinations on Patients*

No.	Name	Diagnosis	Cuff	Sanb.	Syst.	Muff.	Dis.	Cuff	S.G.	Syst.	Muff.	Dis.
1	H. C.	Diabetes	116 / 82–78	126 / 77	+10	−5	−1					
2	A. W.	Hyper. ht. dis.	200 / 118–100	214 / 114	+14	−4	+14					
3	W.	Normal	170 / 90–86	184 / 89	+14	−1	+3	170 / 90–88	196 / 100	+24	+10	+12
4	M.	Arteriosclerosis	100 / 66–60	116 / 55	+16	−11	−5					
5	R. O.	Normal	146 / 70–58	157 / 65	+11	−5	+7	140 / 66–56	152 / 66	+12	0	+10
6	R. M.	Pneumonia	116 / 60–50	127 / 70	+11	+10	+20	116 / 60–50	116 / 63	0	+3	+13
7	E. S.	Nephritis	135 / 90–80	146 / 79	+11	−11	−1	135 / 90–80	166 / 100	+21	+10	+20
8	McN.	Arteriosclerosis	108 / 60–56	137 / 69	+29	+9	+13	108 / 60–56	128 / 68	+20	+8	+12
9	B.	Hyper. ht. dis.	240 / 126–102	253 / 138	+13	+12	+36	234 / 140–130	250 / 142	+16	+2	+12
10	S.	Arteriosclerosis	166 / 90–80	161 / 79	−5	−11	−1	166 / 90–80	183 / 96	+17	+6	+16
11	J.	Arteriosclerosis	220 / 94–0	246 / 84	+26	−10	+84	212 / 90–0	236 / 83	+24	−7	+83
12	S. M.	Normal	136 / 76–68	154 / 73	+18	−3	+5	142 / 72–68	148 / 71	+6	−1	+3
13	L. T.	Arteriosclerosis	204 / 98–86	208 / 100	+4	+2	+14	200 / 98–90	194 / 94	−6	−4	+4
14	R. McK.	Arteriosclerosis	145 / 68–56	173 / 72	+28	+4	+12	145 / 68–60	158 / 71	+13	+3	+11
15	W. S.	Mult. myeloma	130 / 75–68	135 / 69	+5	−6	+1	130 / 75–68	132 / 73	+2	−2	+5
16	F. L.	Arteriosclerosis	130 / 75–68	141 / 55	+21	−23	−19	120 / 78–74	128 / 54	+8	−24	−20
17	C. W.	Normal	130 / 85–80	139 / 75	+9	−11	−7	130 / 86–82	142 / 79	+12	−7	−3
18	H. H. K.	Cirrhosis	120 / 50	128 / 49	+8	−1	−1	120 / 50	122 / 50	+2	0	0
19	C. F.	Cor pulmonale	150 / 85-60	147 / 77	−3	−8	−17	160 / 90–80	145 / 75	−15	−15	−5
20	W. I.	Arteriosclerosis	118 / 70–60	125 / 58	+7	−12	−4					
21	T. H.	Arteriosclerosis	152 / 90	194 / 80	+42	−10	−10					
22	M. I.	Normal	116 / 62	152 / 48	+32	−14	−14	120 / 64-60	133 / 67	+13	+3	+7
23	E. L.	Hemiplegia	154 / 76–70	200 / 84	+40	+8	+14	160 / 80–70	154 / 75	−6	−5	+5
24	H. L. H.	Normal	112 / 64–52	126 / 65	+14	+1	+13					
25	P. A.	Normal	110 / 60–54	128 / 56	+18	−4	+2					
26	N. E.	Normal	120 / 70–64	152 / 72	+32	+2	+12					
27	G. B.	Normal	125 / 80–75	125 / 75	0	−5	0					
28	A. W.	Arteriosclerosis	130 / 72–65	138 / 57	+8	−15	−8					

TABLE 1.—*Continued*

No.	Name	Diagnosis	Cuff	Sanb.	Syst.	Muff.	Dis.	Cuff	S.G.	Syst.	Muff.	Dis.
29	M. C.	Investigation	160 / 85–80	146 / 69	−14	−16	−11	160 / 85–80	132 / 66	−28	−19	−14
30	J. W.	Arteriosclerosis	125 / 55–45	158 / 38	+23	−17	−7					
31	J. R. E.	P. V. disease	110 / 70–0	107 / 62	−3	−8	+62	110 / 70–0	111 / 65	+1	−5	+65
32	M. E.	Arteriosclerosis	126 / 68–62	138 / 72	+12	+4	+10	126 / 70–62	120 / 64	−10	−6	+2
33	T. A.	Paget's disease	134 / 70–66	128 / 58	−6	−12	−8	140 / 70–66	133 / 55	−7	−15	−11
34	A. H. S.	Arteriosclerosis	160 / 76–60	161 / 64	+1	−12	+4	160 / 75–60	163 / 75	+3	0	+15
35	S. E. E.	Normal	134 / 60–52	130 / 60	+4	0	+8	124 / 58–50	100 / 48	−24	−10	−2
36	S. O.	Rheum. ht. dis.	146 / 74–68	158 / 77	+14	+3	+9	142 / 76–66	150 / 75	+8	−1	−9
37	M. A.	Hemiplegia	96 / 50–40	117 / 52	+21	+2	+12	90 / 50–40	112 / 54	+22	+4	+14
38	H. G. A.	Arthritis	130 / 80–66	126 / 67	−4	−13	+1	130 / 80–66	110 / 62	−20	−18	−4
39	L. O.	Hyper. ht. dis.	200 / 106–96	204 / 100	+6	−6	+2	198 / 106–98	171 / 100	−27	−6	+2
40	J. H.	Arteriosclerosis	160 / 72–68	196 / 64	+32	−12	−6	164 / 76–70	183 / 88	+19	+12	+18
41	J. W. F.	Normal	126 / 70–64	146 / 75	+20	+5	+11	126 / 70–64	121 / 61	−5	−9	−3
42	B. A.	Rheum. ht. dis.	118 / 40–0	124 / 58	+6	+18	+58					
43	J. C.	Cor pulmonale	120 / 56–0	114 / 53	−6	−3	+53					
44	G. R.	Arteriosclerosis	140 / 70–65	150 / 52	+10	−18	−13					
45	B. McP.	Cong. ht. dis.	130 / 54–0	100 / 50	−30	−4	+54					
46	A. D.	Arteriosclerosis	140 / 80–78	176 / 88	+36	+8	+10					
47	P. R.	Syphilis	170 / 65–0	190 / 60	+20	−5	+60					

Abbreviations:

Hyper. ht. dis.—hypertensive heart disease; Mult. myeloma—multiple myeloma; Sanb.—Sanborn; Syst.—systolic; Muff.—muffle; Dis.—disappearance; S. G.—strain gauge; P. V. Disease—peripheral vascular disease; Rheum. ht. dis.—rheumatic heart disease; Cong. ht. dis.—congenital heart disease.

ter readings, taken as a standard. Such observations as $\frac{118}{(40–0)}$ indicate no disappearance of sounds in diastole. On the other hand, a reading such as $\frac{88}{60}$, means that no preliminary muffling of sounds was noted before the final disappearance of sounds of Korotkow.

Systolic Pressures. A statistical analysis (analysis of variance)[4] of the data shown in table 1 reveals that the electromanometer reads slightly higher than the strain-gauge manometer in the majority of cases, and that both manometers show the same variability. The mean electromanometric reading was highly significantly greater than the other mean readings. It exceeded the cuff readings by approximately 12 mm. Hg and the strain-gauge values by 8 mm. Hg (table 3).

Analysis of the data by the coefficient of

correlation[4] shows that the correlations between corresponding cuff and electromanometer readings, between corresponding cuff and strain-gauge readings, and between strain-gauge and electromanometer readings in the same patients, were practically the same (table 2). It should be pointed out that the strain-gauge and electromanometer are compared on the basis of 30 patients who had readings taken on both manometers. While the correlation between systolic manometric measurements in each individual is good (.92),

TABLE 2.—*Table of Correlations for Part I*

Comparison	No. of Pairs	Correlation Coefficient
Systolic		
Cuff versus Sanborn	47	0.89
Cuff versus strain-gauge	30	0.89
Sanborn versus strain-gauge	30	0.92
Successive cuff readings	30	0.99
Diastolic		
Cuff muffle versus Sanborn	47	0.88
Cuff muffle versus strain-gauge	30	0.89
Sanborn versus strain-gauge	30	0.88
Cuff disappearance versus strain-gauge	30	0.64 (0.85)
Cuff disappearance versus Sanborn	47	0.57 (0.82)
Successive cuff disappearances	30	0.96
Successive cuff muffles	30	0.99

it is not as good as the correlation between repeated cuff readings (.99), again illustrating variations which may occur with electrical manometric technics. These two correlation coefficients are significantly different.

Diastolic Pressures. The difference between the two manometer readings on diastolic recordings is not significant (the means being only 1.5 mm. Hg apart on 30 patients) as compared with the highly significant difference seen with systolic readings. The disappearance of sound is significantly lower (7 mm. Hg) than diastolic pressures recorded by either manometer, and in one instance out of the 30 sets analysed the disappearance of sound reached 0 mm. Hg. The muffle of sound, however, was found to be higher (3 to 4 mm. Hg) than the diastolic pressure measured by either manometer. This elevation is not significant. In this work, the muffle reads closer to the diastolic manometric pressure than the disappearance (table 3). Furthermore, the

TABLE 3.—*Experimental Means*

Part I

	Systolic S.E.D. = 2.5	Diastolic S.E.D. = 2.5		
		Manometer	Muffle	Disappearance
1st cuff reading	146.8		77.0	65.7
Electromanometer	158.2	73.2		
Strain gauge	150.0	74.7		
2nd cuff reading	145.9		77.8	67.5

Systolic: Electromanometer mean is highly significantly different from the other three means.

Diastolic: Both disappearance means are significantly different from the other four means which, between themselves, are not significantly different.

Part II

	Cuff Readings					
	Systolic		Diastolic			
			Muffle		Disappearance	
	Mean	S.E.D.	Mean	S.E.D.	Mean	S.E.D.
Pre-exercise						
Group mean	112.3	2.75*	76.8	1.85	67.1	2.9†
Physician A	113.1		76.1		65.2	
Physician B	114.8	1.95*	74.5	2.6	67.1	3.5
Physician C	109.1		79.7		68.9	
1st order	112.9		78.1		68.0	
2nd order	115.4	1.95†	78.0	2.6	67.5	3.5
3rd order	108.6		74.3		65.7	
Postexercise						
Group mean	133.8	2.75*	74.0	1.85	53.7	2.9†
Physician A	141.1		74.0		42.6	
Physician B	130.5	5.7	71.3	3.1	58.7	5.4†
Physician C	129.9		76.7		59.7	
1st order	143.8		82.1		61.7	
2nd order	135.6	5.7†	72.8	3.1†	50.7	5.4*
3rd order	122.0		67.1		48.7	

* The bracketed means are significantly different.

† The bracketed means are highly significantly different.

All figures are mm. Hg.

S.E.D. = standard error of difference between means = square root of (twice the residual variance divided by n.).

coefficient of correlation of successive muffle readings is 0.99 as compared with 0.96 on cuff disappearance; this is significantly different. Moreover, there is a better correlation between cuff muffle and either manometer than between cuff disappearance and either manometer reading. It should be noticed that the table records two values of the correlation coefficient for both correlations between disappearance and electromanometer. The bracketed values are the result of considering zero disappearance to be the same as the muffle, only replacing the last digit by zero; for example, 94-0 was changed to 94-90. There was one such case in the 30 sets of readings and five additional cases in the group of 17 patients on whom electromanometer but no strain-gauge readings were taken. Although this greatly increases the correlation coefficients to the point of not being statistically significantly different, they are, in both instances, appreciably lower than the corresponding muffle correlation coefficients. This calculation was done to remove any possible bias in the selection of patients with obvious discrepancy in their disappearance readings. From the above it is concluded that muffle of sounds is superior to disappearance of sounds as an indirect index of diastolic blood pressure.

To digress for a moment, mention may be made of an analysis of the end digits of all cuff readings. It was found that the number of readings ending in zero or five far exceeded the number that could be expected by chance, despite the fact that unusual care was used in the determinations. It would appear, therefore, that blood-pressure readings, even under the best conditions, can be read only to the nearest 5 mm. Hg by an experienced individual.

Part II

To assess the effect of a varying physiologic state upon the human systolic and diastolic blood pressure, indirect blood-pressure readings were taken on each member of a group of 15 healthy young female nurses, by each of three experienced physicians, both before and after a standard exercise test. Each physician was supplied with a mercury-type sphygmomanometer for his own observations. In carrying out the exercise test, the subjects were required to run up and down two flights of stairs, a total of approximately 50 steps. Pre-exercise determinations were carried out after an initial resting period for the group of 20 minutes; postexercise observations were made as quickly as possible after completion of the exercise test. The order in which each subject's blood pressure was recorded by a particular physician, was permutated according to a prearranged plan, which was supervised during the actual determination of blood pressures. Data sheets were designed in such a way as to prevent participating physicians from seeing any previous readings.

It might be emphasized here that with the method outlined above, three sets of 15 blood-pressure readings were obtained both before and after exercise, one from each physician.

The individual blood-pressure readings, pre- and postexercise, were classified by physician and by the order in which they were taken. In the subsequent discussion, the term "order" will imply time differential within a group of either pre- or postexercise readings, and the term "order means" will imply the average of the first, second or third sets of readings, regardless of physician.

In table 4 are arranged the blood-pressure readings obtained by each physician, on each member of the group, both before and after exercise. Statistical analysis of these data, establishes the following.

Systolic Pressures

In the estimation of systolic blood pressure, physicians differed significantly before, but not after, exercise. Although the difference between the means of the individual physicians almost doubled (from 6 mm. Hg pre-exercise, to 11 mm Hg postexercise), the total variance of the postexercise group was five times that of the pre-exercise group. The order means rose, then dropped significantly (7 mm Hg) in the initial phase of the study. After exercise, the drop from the first to the third order means increased to 22 mm. Hg, the third order mean being higher than any order mean of the pre-exercise group (minimal difference 7 mm. Hg).

Of the above, the only point requiring some

explanation, is the absence of any significant difference between physicians in the estimation of systolic blood pressure after exercise. A possible reason for this finding, apart from chance, may be the effect of exercise in rendering louder and more distinct the sounds of Korotkow, thus enabling this group of physicians to agree more closely as to the point at which the sounds begin.

TABLE 4.—*Effect of Exercise on the Blood Pressure*

	Sh	Ro	Cu	Bru	Co	Mc	Pa	Bro	We	Ha	Th	Ba	Pe	An	Lo
							Before Exercise								
Physician I	1 104 76 68	2 108 60 52	3 108 80 72	3 120 70 58	2 100 62 50	1 110 80 70	3 108 76 62	1 122 96 86	2 106 80 72	3 106 90 82	1 102 80 72	2 90 88 80	3 122 100 70	1 112 86 80	2 118 74 60
Physician II	2 110 80 80	3 120 80 54	1 110 80 60	1 110 60 40	3 104 60 40	2 110 80 74	1 110 80 76	2 128 90 70	3 132 88 82	1 118 80 76	2 100 64 50	3 96 70 64	1 110 80 80	2 112 70 60	3 126 80 72
Physician III	3 102 80 76	1 120 75 70	2 115 80 70	2 124 68 60	1 104 58 48	3 115 80 74	2 122 78 68	3 122 80 70	1 112 85 80	2 118 60 45	3 100 62 58	1 114 74 70	2 124 88 82	3 110 70 62	1 120 80 74
							After Exercise								
Physician I	1 108 80 74	2 104 74 50	3 142 76 70	3 152 74 48	2 120 58 36	1 122 76 60	3 162 96 88	1 158 88 80	2 124 74 52	3 144 76 58	1 132 78 62	2 94 76 68	3 136 80 62	1 140 80 38	2 110 64 50
Physician II	3 160 60 35	1 110 80 76	2 120 60 30	3 136 70 54	1 150 74 5	3 116 70 58	2 164 80 5	3 144 80 70	1 190 96 60	2 150 70 5	3 120 50 5	1 136 80 62	2 130 70 44	3 120 70 40	1 170 100 70
Physician III	2 120 90 80	3 136 72 58	1 110 70 66	1 126 70 60	3 138 55 30	2 160 98 90	1 148 70 55	2 160 80 76	3 160 74 70	1 118 55 30	2 115 72 40	3 110 64 60	1 116 65 55	2 110 60 40	3 130 75 70

The numbers in the upper left-hand corner refer to the order in which that particular observation was obtained on a patient by the physician.

Diastolic Muffling

The analysis revealed no significant differences between group means, between physicians before or after exercise of subjects, and between pre-exercise order means. Although the group

means did not differ, the first order mean, post-exercise, was 5 mm. Hg higher than the pre-exercise group mean, and the third order was 10 mm. Hg less; a highly significant drop of 15 mm. Hg in all. In other words, the postexercise order means straddled the pre-exercise group mean (fig. 2).

Diastolic Disappearance of Sound

Before exercise, no significant difference was found to exist, either between different clinicians, or between the orders of reading. After exercise, however, highly significant differences were found to have developed between the group means (a highly significant drop of 13 mm. Hg pre- and postexercise), between different clinician's estimations of this point, and, also, in relation to the order in which the reading was carried out on the patients in the group.

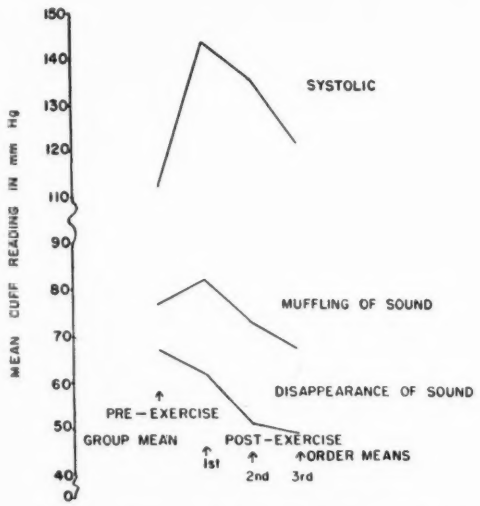

FIG. 2. Relation of order means, postexercise, to group mean, pre-exercise.

The first order mean dropped 5 mm. Hg below the pre-exercise group mean, and subsequent orders showed significant declines from the first order mean (fig. 2).

Observations

Although physiologic disturbance does cause fluctuations in the muffle readings, the pattern is such that the general diastolic level is not appreciably changed. On the other hand, the disappearance of sound goes through the same fluctuations, but the general level of diastolic pressure (by this index) is very definitely lower. The disappearance of sound as a criterion of diastolic pressure is, therefore, felt to be unreliable with any considerable change in physiologic activity. Not only does the actual value for the disappearance drop sharply, but even experienced observers are unable to agree closely, in any individual case, as to just where the sounds of Korotkow disappear.

While it may be argued that considerable exercise is necessary to demonstrate these changes in physically normal individuals, it is obvious that much less exercise (such as climbing the flight of stairs to a doctor's office) may represent an even greater physiologic burden in sick people. Indeed, one not infrequently encounters fit individuals in whom an erroneous diagnosis of aortic incompetence has been made through the acceptance of sound disappearance as the measure of diastolic blood pressure.

DISCUSSION

As stated in the introduction, this work was stimulated by the report of the American Heart Association[1] which, in our opinion, suggests modifications in the technic of blood-pressure determination in humans on the basis of unsatisfactory arguments (found on pages 506–507 of the report). The argument begins with a statement concerning the physical liabilities of the muffle, implying that no such problem exists insofar as the disappearance of sound is concerned. The report states that "a limited number" of observations "strongly suggests" that disappearance of sound, "on the average," conforms "rather better" to the "true" diastolic pressure. The argument continues that "accuracy, not applicability to every individual, should determine the choice of criteria" even though it is agreed that diastolic disappearance (the fifth phase) is known to vary widely, even in normal subjects. The report recommends for these particular cases the use of the muffle (fourth stage) rather than the uncertain disappearance of sound. Subse-

quently, these recommendations state categorically that the muffle is "the less exact" criterion. No reference is quoted for the statement that examiners with differing degrees of auditory acuity agree more closely on the point of disappearance. The argument concludes with the statement, "Frankness must cause us to admit that all too frequently the reading of diastolic pressure by this criterion [muffle] becomes merely a guess."

Consideration should now be given to the publications on which this argument is based. Steele[2] makes the following statements: "The accuracy of the measurements obtained from the optical records of the direct manometer seems unquestionable in theory. Certain practical difficulties leave room for error" (page 1043). "It is obvious that the number of patients in each group is, as yet, far too small to bring out clearly the limits of the indirect method. Although the data are not yet sufficient to permit describing rules for estimating arterial pressure by the indirect method of Korotkow, they suggest that revision of the present empiric criteria may be necessary when sufficient data have been obtained" (page 1045). "In auscultatory technique, the disappearance of sound proved to be a more accurate measure of diastolic pressure than the sudden muffling" (quoted from Steele's summary, page 1049).

Here we have a progression from suggestive evidence to a categoric statement, and it is upon the latter that the American Heart Association committee bases its recommendations.

The practical difficulties which Steele mentions here are precisely those which have been discussed in the body of the present report. A peculiar item in the Steele report is the absence in 41 per cent of 39 cases studied of any determination for the point of muffling. In the present study of 260 readings on 62 patients, in only 1 per cent of readings and 5 per cent of subjects was it impossible to distinguish the muffle from the disappearance.

Furthermore, Steele's report compared direct and indirect data, from different arterial segments. The possibility of anatomic variation and consequent difference in pressure must be considered.

Hamilton and co-workers[3] state: "The indirect method seems to be . . . about 9 mm. high for the diastolic, using the fading of the fourth phase" (page 853). "Experiments show that true systolic and diastolic blood-pressures are not very different from those recorded by the auscultatory method" (page 856). This report is not entirely clear as to just what is meant by the fading of the fourth phase. It would seem that the disappearance of sound was used, but in any case it is evident that both muffle and disappearance were not used, and therefore could not have been compared. In addition, if it is supposed, as seems reasonable, that disappearance was the criterion, then the differences from "true" diastolic pressures cannot be reconciled with those found by Steele. Moreover, no description of the method used in obtaining simultaneous direct and indirect recordings, is found in the paper by Hamilton and associates[3]. Here again, little evidence is found to support the argument of the committee.

In essence, the controversy regarding the choice of muffling or disappearance of sounds as an index of diastolic pressure has been an argument over a few millimeters of mercury. Despite the fact that one or other of the criteria may approximate the "true" diastolic pressure more closely on the average, it is felt that the constancy of the relationship between either criterion and the "true" diastolic pressure is of the greater importance. The more constant this relationship, the more accurate the physiologic measurement.

In the present study, data are presented which establish, statistically, that the point of muffle suffers less change than does the disappearance, despite physiologic variations in patients. This data strongly suggests also that the muffle bears a more constant and closer relationship to the "true" diastolic pressure than does the disappearance of sound. Part I demonstrates that one physician is able to repeat muffle readings more accurately, and in part II three physicians agree more closely on muffle values before and after exercise.

An interesting and important observation from this study is the failure of the two manometers used to correlate with one another any more closely than with the sphygomanometer. In theory, correlation should be practically perfect. An inescapable conclusion is that practical difficulties inherent in present-day technics will definitely limit any expected accuracy of such instruments; especially so in the case of the electromanometer, wherein the metal chamber housing the microphone precludes observation of blood clot. Although the sphygmomanometer can only be read to the nearest 5 mm. Hg, it would seem to be as accurate as any available electrical manometer —a finding paralleling the experience of Hamilton and co-workers and Steele with optical manometers.

If we turn to theoretic reasoning and our knowledge of what is happening in the auscultatory method, there is excellent reason for taking the change in the sound rather than its disappearance. Sound in flowing blood means that turbulence is present, and turbulence depends on the velocity of flow and the size of the orifice, that is, the orifice of the artery compressed under the cuff. Disappearance of the sound denotes that turbulence has ceased, as the artery widens when the cuff pressure falls. To our knowledge, no reason has ever been advanced why the disappearance of turbulence should have any relation to the diastolic pressure, other than a purely accidental one, in normal subjects at rest. There is, on the contrary, a very good reason why the sound should change in character when the cuff pressure reaches and falls below the diastolic pressure. At that point, the stream of blood through the compressed artery is no longer completely interrupted at the end of diastole, but some blood passes through at all times in the cardiac cycle.

The possibility of serious errors in the readings by the cuff method, because the pressure in it has not been efficiently transmitted to all the tissues beneath it, has been recognized; but this error will affect both criteria of diastolic pressure alike. *Both* criteria likewise, must obviously depend upon the auditory acuity of the observer, on the accuracy of the placing of the stethoscope head, and on efficient conduction in the stethoscope tubing. Thus, all theoretic considerations combine to suggest the adoption of the muffling, or change in the sound rather than its disappearance, as a criterion of diastolic pressure. The data presented in this paper support this hypothesis.

Conclusion

The two experiments suggest that the muffle is the better index of diastolic pressure, in disagreement with cited papers which are themselves only suggestive. For this reason, it is recommended that a larger series of subjects be studied and that a far greater number of participating clinicians be included in such a project.

It would seem unwise to replace an accepted standard by one which, on the basis of present evidence, does not seem to be nearly as good.

Summary

1. In part I of this study, simultaneous indirect and direct blood-pressure measurements are compared in 47 patients. Of this group, 30 patients had direct intra-arterial measurement of blood pressure recorded on two electrical manometers.

2. In part II, the effect of exercise on the muffle and the disappearance of sound as indexes of diastolic pressure, as studied by three physicians in a group of 15 patients, is presented.

3. The results of statistical analysis of these data are presented.

4. A criticism of the recommendations of the American Heart Association regarding determination of blood-pressure, is included.

5. Recommendations are made suggesting further work.

Acknowledgments

The authors sincerely thank Dr. J. Lewis, Head of Medicine, Department of Veteran's Affairs Westminster Hospital, for his co-operation in obtaining much of the clinical material for this study. Dr. A. Burton, Professor of Biophysics, University of Western Ontario, was most helpful in reviewing the manuscript. We also wish to thank Mr. G. Steward for his excellent technical assistance in carrying out this work.

Sumario Español

En este estudio una comparación se ha hecho entre los métodos directo e indirecto de obtener la presión arterial. Un analisis estadístico de los datos sostiene el punto de vista de que el apagamiento de los sonidos, o la cuarta fase de Korotkow, conlleva una relación más cercana y constante a la presión diastólica determinada directamente. Este estudio, por lo tanto, recomienda la aceptación del apagamiento de los sonidos de Korotkow como la medida de la presión diastólica.

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Parasystole

By ALFRED PICK, M.D.

Five instances of parasystolic rhythm are presented in which detailed analysis revealed some particular physiologic aspect pertinent to the understanding of this type of disturbance of rhythm. In four cases the ectopic parasystolic focus was localized in the ventricles and in one in or near to the A-V junction; in two of the former instances the site of the ectopic focus appeared to be the interventricular septum. The mechanism of protection of the parasystolic center, while not identical in every case, might be effected by an area of true block, as exemplified by one instance. Parasystole offers the rare opportunity to determine the refractory phase of the A-V junction or of the ventricular myocardium in the human heart. Occasionally parasystolic rhythm may appear in association with other types of manifest multiple cardiac pacemakers and produce very complex arrhythmias, which can be resolved by application of known physiologic principles.

NORMALLY, rhythmic contraction of the entire heart is initiated and maintained by a single pacemaker, the sinus node. It dominates all other potential pacemakers by virtue of its relatively faster rate of cyclic discharge. Simultaneous activity of two cardiac pacemakers occurs in A-V dissociation; here, each pair of chambers, the auricles and ventricles, is governed entirely, or for the most part, by its own pacemaker. Rarely, two rhythmic and completely independent pacemakers operating at different rates can be seen to be in competition for the activation of the ventricles or of the auricles. Such a condition is termed parasystole.

Fleming who conceived this type of disturbance of cardiac rhythm while analyzing polygraphic curves[1] was aware of the basic problem involved, namely, to account for the undisturbed activity of the slower cardiac center in a chamber which, at the same time, responds to stimuli from another faster center. Since then, based on the electrocardiogram, a number of clinical instances[2-28] of parasystolic rhythm has been reported as well as similar observations in the experimental animal.[29-32] Temporary or permanent "immunity" of a subsidiary pacemaker to impulses of the dominant rhythm has been accepted as a fact although its explanation remains controversial.

The present report deals with some observations bearing on the mechanism of parasystole. Five electrocardiograms which satisfy criteria postulated[31, 33] for the diagnosis of parasystolic rhythm were analyzed. The methods used for analysis and the conclusions which were derived are described in the legends of figures 1 to 5 and this approach can be followed by studying the corresponding diagrams. Each case illustrates a particular physiologic aspect of parasystolic rhythm.

Thus, figure 1 presents an example of ventricular parasystole in its "purest" form with its implications concerning the operation of the refractory period and of interference. In figures 2 and 3 the site of a ventricular parasystolic focus appears to be revealed by a consideration of the contour of ectopic and dominant beats; moreover, figure 3 seems to provide some clue as to the mechanism of "protection" of such a parasystolic ectopic focus. In figure 4, a parasystolic focus in, or close to, the A-V node appears to be shielded from other impulses passing the A-V junction in both directions. Factors responsible for the apparent irregularities of the manifestation of this parasystolic pacemaker are revealed by detailed analysis, and the duration of the refractory phase of A-V junctional tissues can be estimated closely. Finally, in figure 5, the unusual combination

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Aided by the Sam and Sarah Ehrlich Memorial Fund for Cardiovascular Research and the Michael Reese Research Foundation.

of ventricular parasystole and re-entry is seen in the same tracing, and the association of parasystole with an incomplete A-V dissociation aptly illustrates the fundamental difference in the two apparently similar mechanisms.

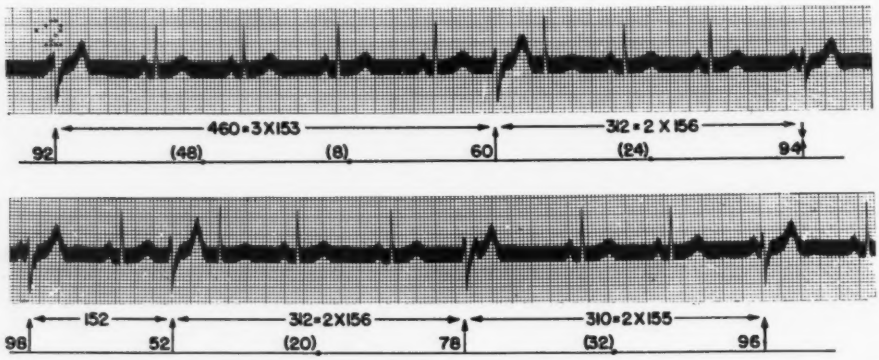

FIG. 1. *Ventricular parasystole with simple interference.* The conventions in the diagram below the tracing are as follows: The lower horizontal line represents the ectopic ventricular focus. Its manifest discharge (corresponding to the premature beats in the electrocardiogram) is indicated by the upwards directed vertical arrows, its ineffective (latent) discharge by the dots. The simultaneous short vertical arrows pointing towards each other (at the end of the top strip) represent simultaneous activation by a sinus node and an ectopic ventricular impulse (a ventricular fusion beat). The values within the horizontal arrows (upper line) indicate the temporal sequence of the ectopic impulses; the longer intervals are also given as multiples of the short ones. The values just to the left of the vertical arrows (lower curve) are the time intervals between premature beats and the last preceding sinus beat (manifest coupling); the values in parentheses just to the left of the dots are similar time intervals in the case of the latent discharges of the ventricular focus (latent coupling). All time values represent the number of hundredths of a second.

The two tracings are successive portions taken from a long strip of lead II. The slightly irregular sequence of sinus beats (51 to 70 per minute) is disturbed by premature ventricular complexes. With the exception of the last beat in the upper strip, which is intermediate in contour between the normal and ectopic beats, all have the same bizarre contour with QRS prolonged, revealing their ventricular origin. As evident from the diagram, the coupling of the premature beats to the preceding sinus beat varies considerably (0.52 to 0.96 second), resulting in interpolation of the beats with the shorter coupling, and a ventricular fusion beat on occasion of the longer coupling. The long intervals between two ectopic beats are multiples of the shortest ones. All this indicates the presence of a ventricular parasystolic focus operating at a rate of 38 to 40 per minute. As determined in the entire tracing, and exemplified in the two short strips shown, this ventricular pacemaker becomes manifest in the form of a premature beat whenever its discharge follows activation of the ventricles by a sinus impulse by 0.52 second or more, and its discharge remains latent whenever this interval is 0.48 second or less. Thus, in this case, the only factor dominating the manifestation of the slower impulses of the ventricular pacemaker is simple interference which results from the refractory phase of the ventricles after each stimulation by the more rapid impulses from the sinus node. The duration of ventricular unresponsiveness (0.48 to 0.52 second) is considerably longer than that of the Q-T interval (0.40 second) of the sinus beats.

COMMENT

The Diagnosis of Parasystole

Typically, parasystole is manifested in the electrocardiogram by the appearance of auricular or ventricular premature beats of more or less aberrant contour depending on the site of ectopic impulses formation. Contrary to the common variety of premature beats, their coupling with the preceding dominant beats varies widely and leads to interference of dominant and ectopic impulses at various levels.[4] Thus, compensatory pauses, interpolation and fusion beats can usually be seen in the same tracing (figs. 1 and 2). This, however, as has been

shown in this department,[34] may occur also in the absence of parasystole. In order to prove the latter, the presence of an autonomous ectopic rhythm, different in rate from that of the dominant pacemaker, must be demonstrated. If the rate of the normal beats is slower[3, 9, 24, 25, 31] or temporarily depressed,[21, 26, 28] then the parasystolic cycle may be measured directly by the time of appearance of two or more successive ectopic beats (fig. 4).

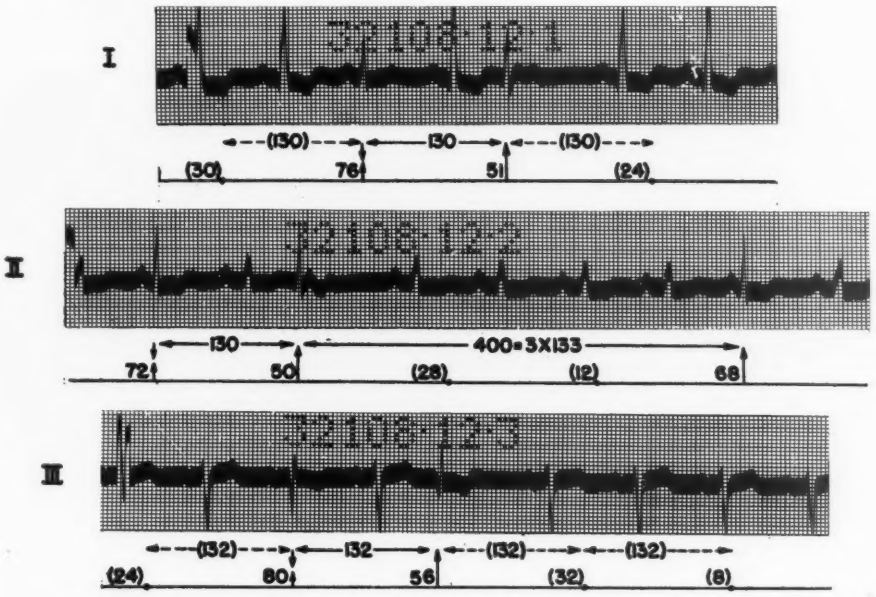

FIG. 2. *Parasystole originating in the interventricular septum.* The conventions in the diagram are the same as in figure 1. In addition, the values in parentheses between interrupted horizontal arrows (upper line) are the temporal sequence calculated for latent discharges of the ventricular focus.

There is a regular sinus rhythm (76 per minute) with occasional premature beats. The QRS duration of the sinus beats is 0.12 second and its contour in all the leads (including precordial) suggests a minor left sided intraventricular conduction defect. By contrast, the QRS duration of the premature beats is normal (0.09 second). The latter appear (a) at varying intervals—the long one in lead II, for example, is three times as long as the short ones in this and in other leads; (b) with varying coupling to the preceding sinus beat (0.56 to 0.80 second)—the longest ones result in ventricular fusion beats. Thus, a parasystolic pacemaker with a discharge rate of 45 to 46 per minute is present. The refractory phase of the ventricles, as far as it can be determined in these three short strips, is somewhere between 0.32 second (the longest coupling of a latent discharge) and 0.50 second (the shortest coupling of a manifest discharge). The shorter QRS duration of the ectopic beats compared with that of the sinus beats suggests that the parasystolic focus is located distal to a lesion blocking intraventricular conduction, at a point approximately equidistant from both bundle branches, most likely in the interventricular septum.

This is done when (a) the intervals separating ectopic beats can be reduced to a least common denominator corresponding to the cycle length of the parasystolic ectopic rhythm and (b) all ectopic impulses which occur after the end of the refractory phase following dominant beats become manifest in the record (figs. 1 to 5).

The Localization of the Parasystolic Focus

While it has been stated[23] that supraventricular parasystolic rhythm, especially in the A-V node, is rare, several such cases are on record,[9, 20-22, 28] and one is illustrated in figure 4. Unlike ventricular parasystole, the nodal type seems

to occur in cases without clinical evidence of heart disease.

As in paroxysmal tachycardia,[35] supraventricular origin could be postulated in any case of parasystole if the assumption is made that there is aberrant spread of the ectopic impulse through the ventricular myocardium. However, in most instances, the constant contour of the ectopic ventricular complexes, despite marked variations of their coupling to the preceding beats, is against such an interpretation. On the other hand, the absence of ventricular fusion beats, as in figure 3, does not necessarily prove supraventricular origin of the ectopic rhythm.

Premature beats in the presence of an intraventricular conduction defect may occasionally exhibit a more normal contour, and/or QRS complexes shorter in duration, than the normal beats (figs. 2 and 3). Such observations have been subject to various interpretations. Persistence of the phenomenon in the face of marked variations of the coupling of the premature beats renders supernormal phase of intraventricular conduction[36, 37] a less likely explanation than localization of the ectopic focus to the interventricular septum as proposed in this report and previously by us[25, 39] and by others.[38]

Retrograde conduction of the parasystolic impulse to the auricles could be used to favor its localization within the A-V node. However,

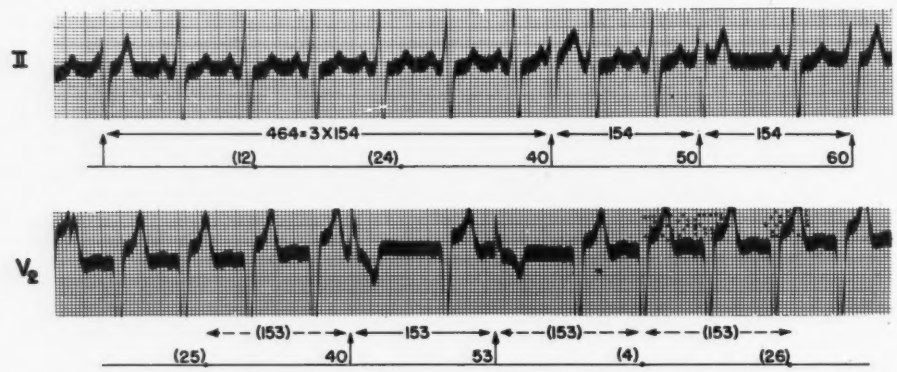

FIG. 3. *Ventricular parasystole with demonstration of protection block, both in the left bundle branch.* The conventions in the diagram are the same as in figures 1 and 2.

Regular sinus beats (rate 88 per minute) have widened QRS complexes (0.14 second) and, in V_2, a contour usually seen with left bundle branch system block. (This was confirmed by the appearance in the other leads of the entire tracing, which included a long strip of lead II.) Premature beats with the appearance characteristically seen in right bundle branch system block (see V_2) but with less prolonged QRS complexes (0.10 second) occur with varying coupling to preceding sinus beats. The long interval separating two premature beats in the first portion of lead II is a multiple of the remaining shorter ones shown. Thus, a parasystolic pacemaker discharging at a regular rate of 39 per minute appears to be operating in the left ventricle distal to a blocking lesion in the left bundle branch. Its impulses remain latent when they occur less than 0.40 second after a sinus beat. The fourth ventricular complex from the end in lead V_2 is a sinus beat. Its QRS begins only 0.04 second before the expected parasystolic impulse; yet the ventricular fusion beat anticipated in the presence of left bundle branch block under these circumstances (25) does not occur. Evidently, here, the short time of 0.04 second permitted the sinus impulse to reach the left ventricle via the interventricular septum and to prevent the activation by the parasystolic pacemaker.

A fusion beat in parasystole may fail to occur at the expected time if the sinus and ectopic impulses share a common pathway during activation of the particular ventricle which is the seat of the ectopic pacemaker. This consideration together with that of the contour and QRS duration of the sinus and ectopic beats suggests that the parasystolic pacemaker in this instance is located (a) in, or close to, the main left bundle branch and (b) in a region which is "protected" from the faster sinus impulses by an area of depressed unidirectional conduction.

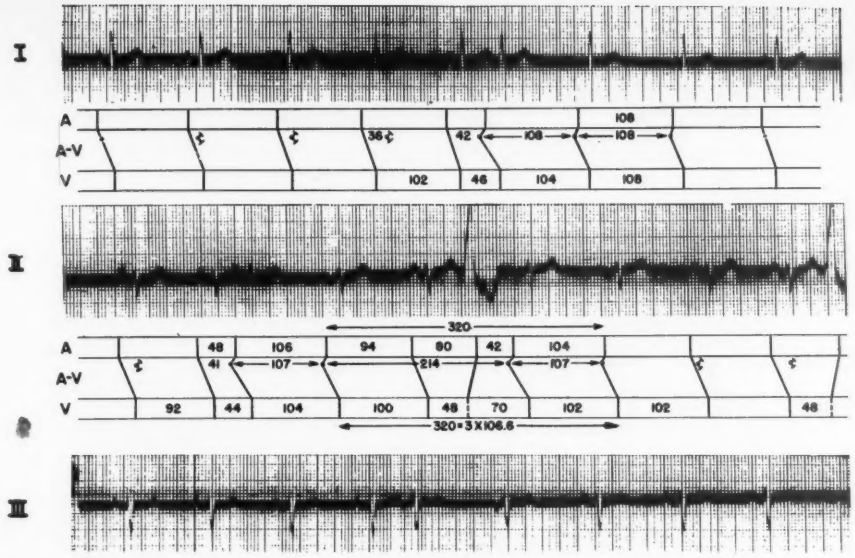

FIG. 4. *Supraventricular (nodal) parasystole with demonstrated bidirectional protection.* The convention in the diagrams are as follows: The vertical lines at the level of A indicate auricular activation; the solid vertical lines at the level of V, activation of the ventricles by a supraventricular impulse; the interrupted vertical lines at the level of V, activation by an idioventricular impulse. Figures between lines at the level of A and V represent the time sequence between neighboring auricular and ventricular beats respectively. Supraventricular impulses originating in or near the A-V junction are indicated by dots at the level of A-V, and intervals separating them are indicated by figures within horizontal arrows. The oblique lines at the level of A-V stand for conduction of impulses from auricles to ventricles or vice versa; the varying of inclination of these lines indicates varying speeds of conduction of the impulses through the A-V junctional tissues; short lines at right angles to them, blockage of the impulse. A figure to the left of a dot (at the level of A-V) gives the calculated time interval between a nodal impulse and the last preceding sinus impulse crossing the A-V junction. The time values are as in figure 1.

Three types of ventricular activation are seen: (1) impulses arising in the sinus node at a rate varying between 59 and 65 per minute and with a P-R interval of 0.18 second; (2) impulses arising in or near the A-V junction activating not only the ventricles but also, in retrograde fashion, the auricles as evidenced by inverted P waves in leads II and III preceding normal QRS complexes at varying intervals; (3) premature ventricular complexes of bizarre configuration originating in the ventricles, likewise transmitted in retrograde direction to the auricles. While the coupling of the ventricular ectopic impulses to the preceding beats is fixed (0.48 second) that of the supraventricular ectopic impulses is not. This is due to (a) premature appearance of some of the latter, and (b) delay in their forward and retrograde conduction. The rate of discharge of the ectopic nodal pacemaker (55 per minute) can be determined by measuring the intervals between nodal beats having equal P-R intervals—for example the interval between the seventh and eighth beat in lead I (1.08 second) and between the fourth and eighth beat in lead II (3.20 second or 3 × 1.07 second). The latter is a multiple of the former. On the assumption that sinus as well as nodal impulses that follow after long pauses are conducted through the A-V junction at the same rate of speed, the time of discharge of additional nodal impulses can be calculated. Thus, for example (see diagram), the time of nodal discharge responsible for the sixth complex in lead I is defined by the interval between the QRS before and that after this beat (0.46 plus 1.04 second) minus 1.08 second, the cycle between nodal impulses. This makes the time interval separating this nodal discharge from the time at which the preceding sinus impulse traverses the A-V junction 0.42 second. Using the cycle length 1.08 second as that of the regular parasystolic nodal pacemaker, permits location of its several discharges in this lead (indicated by dots in the diagram). A similar method can be employed in leads II and III. In lead II a cycle length of 1.07 second is used for the parasystolic nodal pacemaker (see diagram).

Nodal impulses occurring 0.41 second, or later, following passage of a sinus impulse through the A-V junction are transmitted to both auricles and ventricles, whereas those occurring 0.36 second, or less, after a sinus impulse passage are not conducted and remain latent. Thus the refractory phase of the A-V junctional tissues can be determined within the narrow range of 0.05 second. Furthermore analysis shows that neither the impulses transmitted from the sinus node nor the retrograde ones initiated by the premature ventricular beats disturb the regular action of the nodal parasystolic pacemaker. There is thus protection of the nodal parasystolic pacemaker from impulses from above and from below while it itself can transmit impulses in both directions (except for the refractory period).

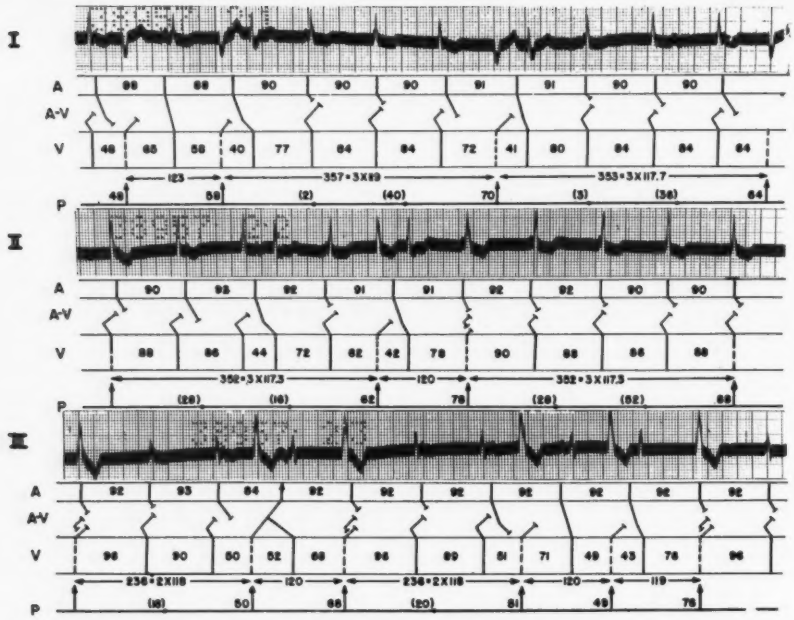

FIG. 5. *Ventricular parasystole (with retrograde conduction and a reciprocal beat) associated with incomplete A-V dissociation due to nodal tachycardia.* In the diagram below each lead, the conventions in the upper part (labeled A, A-V and V) are the same as used in figure 4, while those in the lower part (labeled P) are the same as in figs. 1 to 3. Three types of ventricular activation are seen in leads I and II and four types in lead III. Impulses are present which arise in a ventricular parasystolic pacemaker with a discharge rate of 49 to 51 per minute, but only those coming 0.48 to 0.51 second or more following a supraventricular impulse become manifest in the form of more or less bizarre appearing beats (best seen in lead III). The tendency for retrograde conduction of these parasystolic idioventricular impulses to occur is evidenced by an instance (fourth and fifth complex combination in lead III) where such an impulse not only reaches and activates the auricles in retrograde fashion but also re-enters the A-V junction and causes a reciprocal beat. In addition, this retrograde impulse causes a disturbance of the regular discharge of the sinus node represented by the succession of upright P waves occurring at a rate of 65 to 68 per minute. In fact, this is the only interruption of the sinus rhythm found.

Most of the sinus impulses are prevented from activating the ventricles by interference from a third and faster pacemaker (67 to 71 per minute) arising in the A-V node. Only those auricular impulses reach and activate the ventricles which arrive at the A-V junction after a sufficiently long period to allow for recovery from a preceding impulse, whether conducted in forward or retrograde direction. This latter they do with varying P-R intervals, and with varying degrees of aberrant intraventricular conduction. This last mechanism is, of course, A-V dissociation with ventricular captures.

Penetration into the A-V junction (concealed conduction) of some of the "nonconducted" auricular impulses (first P wave in lead I and seventh P wave in lead III) is suggested by the failure of subsequent idioventricular parasystolic impulse to complete its retrograde conduction into the auricles.

Both the sinus and retrograde ventricular impulses discharge the nodal pacemaker prematurely when they reach it, but the regular action of the parasystolic ventricular focus remains undisturbed owing to some protection mechanism.

At times, for example, the sixth beat in lead I and the second beat from the end in lead III, all three pacemakers—the sinus node, the A-V node and the parasystolic ventricular focus—are discharging almost simultaneously. In such instances only two of these impulses become manifest, while the third (nodal or ventricular) remains latent due to the refractoriness of the junctional tissues or of the ventricular myocardium established by the others.

This type of analysis, therefore, makes an otherwise inexplicable record fit into an orderly scheme.

retrograde spread of ventricular premature impulses is more common than generally assumed,[40] and is demonstrated by figure 5. This figure reveals that even re-entry of the retrograde impulse may be initiated by a parasystolic ventricular focus. Retrograde activation of the auricles may temporarily depress the discharge rate of the sinus node[28] and thus result in spontaneous temporary manifestation of the parasystolic interval. For this purpose, carotid sinus pressure and/or application of cholinergic drugs have been suggested[21] as diagnostic procedures in parasystole.

The "Protection" of the Ectopic Focus

Undisturbed simultaneous activity of two rhythmic centers of different rates, side by side as it were, has been recorded in isolated fibers of the specific muscular system of the heart.[41, 42] While this observation provides strong support in favor of the concept of parasystolic rhythm, the mechanisms by which one rhythmic center is protected from the impulses of others has been a matter of speculation. The idea of an area of unidirectional block surrounding an ectopic focus has been proposed,[20, 29, 33, 42, 43, 44] with allowance for temporary alteration of conditions of entrance and exit of impulses, to account for occasional irregularities of the parasystolic center (see below). Scherf, however, rejects the concept of protection *block*. As a result of extensive experimental and clinical studies on ectopic impulse formation[11, 23, 30, 31, 32] he concludes that guarding of an ectopic center from extraneous impulses can be accounted for by the inherent, manifest or latent rapid rate of its discharge. He states that the main factor determining the type of manifestation of an ectopic center is its excitability in relation to the strength of impulses dominating the rhythm of the heart.

If the interpretation of figure 3 of this report is correct, it can be used in support of the block theory of protection. A depressed area in the left bundle branch, evidenced by the contour of the sinus beats, appears to prevent passage of impulse to, but not from, a slow ventricular pacemaker. Thus, true block not only seems to protect continuous formation of impulses in an ectopic focus but may actually be the factor permitting the original initiation of its activity. In this case Scherf's concept is not necessary.

However, the mechanisms effecting protection of an ectopic center from extraneous impulses may not be the same in every case. In figure 4, which is an instance of nodal parasystole, impulses by-passing a rhythmic pacemaker in two directions are conducted through the A-V junction at normal speed. Hence, an area of regional depression protecting the parasystolic center from discharge appears less likely. Under such circumstances, any ectopic focus could be conceived as operating apart from the normal pathways of forward and retrograde conduction,[5] and as being connected to adjacent structures by fibers with unidirectional conduction. Such a dissociation of functions of the junctional tissues, while hypothetic in our present stage of knowledge, does not seem impossible considering the complex histologic architecture of the A-V node.[45] The same mechanism may also prevail in other parts of the heart and give rise to a parasystolic pacemaker.

The Regularity of the Parasystolic Pacemaker

Regularity of discharge of the ectopic pacemaker is the accepted cardinal sign of parasystole. Thus in figures 1 to 5, the cycles, both those actually measured and those calculated, do not vary by more than 0.05 second, which is within the limits of errors of measurement. If criteria used for the differential diagnosis of paroxysmal tachycardias[35] were applied, much greater variations could be allowed in the case of a ventricular focus, but this would render the diagnosis of parasystole very difficult.[3] As a matter of fact, parasystole has been recognized in the face of an apparent irregularity of its pacemaker by assuming either a temporary "break through" of the impulses of the extraneous dominant pacemaker past the barrier of protection of the ectopic focus (intermittent parasystole),[2, 14, 21, 23, 46] or a temporary release of an "exit block"[9, 15, 16, 30] which had kept many of its impulses confined exclusively to the immediate region of the parasystolic pacemaker. Furthermore, variations in the manifest cycle of the parasystolic beats can be expected with varying degrees of delayed con-

duction of impulses from the ectopic center to the surrounding myocardium such as occurs in second degree A-V block.[4, 7, 12, 14, 15, 29] This latter factor will become manifest in the form of varying A-V conduction times, when the parasystolic focus is located in the A-V node, as in figure 4.

The Determination of the Refractory Period

It is ordinarily impossible to determine exactly the refractory period of the human heart. Parasystole offers the unique opportunity of determining, the duration of the unresponsiveness following stimulation of tissues surrounding the ectopic pacemaker, provided that manifest and latent spacing of ectopic impulses remains regular over a long period of observation. The refractory phase is defined, on one hand, by the longest calculated coupling to the previous beat of a latent ectopic discharge, and, on the other hand, by the shortest of such coupling resulting in a manifest ectopic beat.[4, 10, 14] In the instance illustrated in part in figure 1, the duration of ventricular unresponsiveness could be defined within the limits of 0.05 second. It proved to be considerably longer than the normal Q-T interval which usually is identified with the duration of ventricular refractoriness. While both ventricular refractory period and Q-T duration may vary to a similar degree with variations in rate and, therefore, from case to case (figs. 1, 2, 3, 5), it becomes obvious that the electrical phenomenon of repolarization does not necessarily coincide temporally with a functional phenomenon related to the heart's excitability.

An approximate measurement of the normal and abnormal refractory period of A-V nodal tissues can be obtained in incomplete A-V dissociation by correlating the incidence, and the P-R intervals, of "ventricular captures" with the respective R-P distances. Such calculations, however, have only relative value since neither the exact time of arrival of the auricular stimulus at the A-V junction, nor the point of its interference with the nodal impulse, is known. The procedure indicated in the diagrams of figure 4 represents an attempt to define the refractory period of nodal tissues by a method similar to that used in the case of ventricular parasystole, in the belief that it may yield more exact information in the future, when applied to a larger amount of material.

The Definition of Parasystole

There is no general agreement to which conditions of disturbed cardiac rhythm the term parasystole should be applied. Thus, instances exemplified in this report have been classified by some, together with instances of A-V dissociation, under the common heading of "pararhythms."[6, 47, 48] Occasionally, the two types of disturbance of rhythm may occur in association as shown in this report (fig. 5) and previously.[24] Under such circumstances, the need becomes obvious to define and to distinguish sharply these two apparently similar conditions: One, the "protected" simultaneous activity of two cardiac pacemakers which is parasystole; the other, its "unprotected" counterpart appearing as complete and incomplete A-V dissociation.

Summary and Conclusions

1. The principles of parasystolic rhythm and their implications are discussed on the basis of five selected examples.

2. In two instances of ventricular parasystole, the origin of the ectopic rhythm in the interventricular septum was suggested by comparison of the contour of the ectopic beats with that of the dominant beats. In one of them, the ectopic center appeared localized in, or close to, the left bundle branch and in a region of impaired conduction. In this instance, therefore, the theoretic concept of protection *block* appeared to be substantiated. However, alternative mechanisms in other instances are possible and their relative role may vary from case to case.

3. The presence of a parasystolic center provides the unique possibility of determining in the human heart the duration of the refractory phase in tissues which surround the ectopic pacemaker. In one case of ventricular parasystole, it was found to outlast the electrical activity of the ventricles as determined by the Q-T interval.

4. The occasional association of parasystole with other complex disturbances of cardiac

rhythm requires a sharp distinction between the various types of arrhythmias effected by simultaneous activity of more than a single cardiac pacemaker.

5. The term parasystole refers to those instances of double rhythm of the auricles or of the ventricles in which one pacemaker is "protected" from the impulses of the other.

Acknowledgments

The author is indebted to Drs. L. N. Katz and R. Langendorf for valuable criticisms.

Sumario Español

Se presentan cinco casos de ritmo parasistólico con analisis detallado que revela algún aspecto particular fisiológico pertinente al entendimiento de este tipo de disturbio en ritmo. En cuatro de los casos el foco ectópico parasistólico se localizó en los ventrículos y en uno, en o cerca de la juntura A-V; en dos de los primeros casos la localización del foco ectópico fué en el septo interventricular. El mecanismo de protección del centro parasistólico, aunque no idéntico en cada caso, puede ser afectado por un área de bloqueo, como se demostró en un caso. El parasístole ofrece la rara oportunidad de determinar la fase refractoria de la juntura A-V o del miocardio ventricular en el corazón humano. Ocasionalmente el ritmo parasistólico puede aparecer en asociación con otros tipos de pacificadores cardíacos múltiples manifiestos y produce unas arritmias muy complejas que pueden ser analizadas mediante la aplicación de principios fisiológicos ya conocidos.

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The Effect of a Threshold Electrical Stimulus upon the Repolarization Process of the Left Ventricle of the Intact Dog Heart

By L. H. NAHUM, M.D., H. LEVINE, M.D., H. GELLER, M.D., AND R. SIKAND, M.D.

A threshold stimulus applied either at apex or base of the intact dog ventricle at any depth of the myocardium produces a delay in repolarization during the following three to four normal beats, in an area equivalent to the size of the proximal zone of the precordial lead. This change in repolarization is not caused by postextrasystolic distension of the ventricle. The question is discussed whether a threshold stimulus initiates a propagated disturbance from the point of the electrodes or the larger area whose repolarization is altered.

IN THE COURSE of a study on the excitability cycle of the apex and base of the normal dog heart performed with an intact chest wall and with the heart beating spontaneously in situ,[1] it was observed that after a forced extrasystole the oncoming beats showed T-wave alterations with a definite pattern.

This phenomenon has already received attention from the clinical point of view. Levine and co-workers[2] have pointed out that the T-wave alterations in postextrasystolic beats are most likely to occur in hearts that are already the seat of damage, but that they can be found in a small proportion of normal hearts though not in normal individuals. In speculating on the possible explanations for this phenomenon various authors have suggested several causes:

(1) Changes in repolarization as a result of alterations in cycle length.[3]

(2) Mechanical effects of overdistension of the ventricular wall,[4] particularly in those cases that already suffer from coronary artery insufficiency of either the inner or the outer layers of the myocardium.

The production of forced beats has become an important technic in the study of localization of activity in the heart as well as the spread of excitation through it. In fact, the theory of limited potential differences in regard to the explanation of the ventricular complex was originally propounded on the basis of a study of the configuration of the initial phases of the ectopic beat in endocardial and epicardial stimulation.[5]

The T waves of postextrasystolic beats have received little attention experimentally, since the repolarization process in exposed hearts is subject to alterations from temperature, water, and carbon dioxide changes at the cardiac surface. If the stimulation can be effected in a known region of a normal heart in situ, the repolarization of the ventricle following a forced beat can be studied, and light thrown on the problem of the area involved by a threshold stimulus. It is already known that changes in the local excitatory state can be produced by a subthreshold stimulus,[1] but no evidence on the area involved is at hand. One can make deductions about the size of this area from a study of the T waves following a forced beat, since if changes are present they would be due to involvement of a measurable portion of the myocardium.

METHOD

The apical and basal regions of the hearts of anesthetized dogs were stimulated by means of a bipolar needle electrode inserted into the myo-

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Supported in part by Fluid Research Fund, Yale University School of Medicine and the Connecticut Heart Association.

cardium through the intact chest wall.[1] Threshold stimuli were introduced at two-minute intervals from a rectangular wave generator through a mercury key. The hearts were allowed to beat spontaneously, and by means of a delayer system the stimuli could be introduced at any desired instant in the cardiac cycle. In this communication extrasystoles elicited in the threshold period by stimuli of threshold intensity are reported. The responses were recorded with a Sanborn Tri-Beam Cardiette in a unipolar precordial lead from over the left apex.

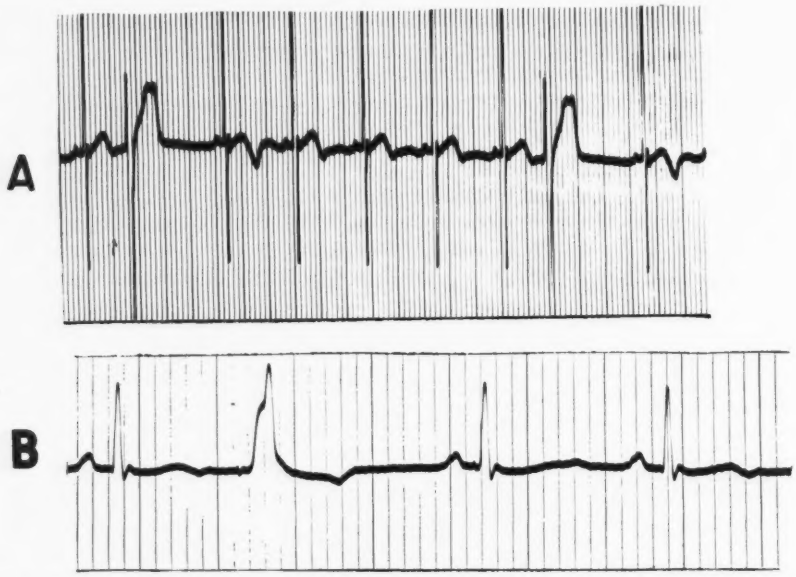

FIG. 1. Extrasystoles and postextrasystolic T-wave changes produced by rectangular wave stimulation in the dog. Unipolar precordial lead from over left apex. In *A*, stimulating electrode at apex of left ventricle, paper speed 25 mm. per second. In *B*, stimulating electrode at base of left ventricle, paper speed 75 mm. per second.

RESULTS

In 27 animals forced beats from stimulation of the left apex were uniformly followed by a compensatory pause, after which the succeeding beats showed inversion of the T wave which progressively decreased in amplitude until the fourth or fifth postextrasystolic beat, at which time the T wave had reverted to its prestimulation pattern (fig. 1*A*).

In experiments in which the ventricular base was the site of origin of the extrasystole, the apical precordial lead did not constantly reveal changes in the configuration of the postextrasystolic T wave. At times alterations of the type seen in figure 1*B* were observed. In this example the T wave in the complex preceding the extrasystole was diphasic, while the succeeding beat exhibited an upright T wave.

The Q-T intervals in the complexes following the extrasystoles were always prolonged, as indicated in the following tabulation:

Apical Stimulation (fig. 1*A*)

Beat preceding extrasystole: .24 second
First beat following extrasystole: .29 second
Second beat following extrasystole: .27 second
Third beat following extrasystole: .25 second
Fourth beat following extrasystole: .25 second
Fifth beat following extrasystole: .24 second

Basal Stimulation (fig. 1*B*)

Beat preceding extrasystole: .26 second
First beat following extrasystole: .29 second
Second beat following extrasystole: .26 second

Discussion

The evidence reported indicates that an electrical stimulus of threshold intensity applied to any region of the ventricle produces a short period of delayed repolarization around the point of application of the shock, as evidenced by an alteration in the T wave of the precordial lead. When the shock is applied underneath the exploring electrode, prolongation of the Q-T interval and conversion of an upright to a sharply inverted T wave takes place in the four or five beats following the extrasystole. This change is transient, and both the Q-T interval and the T wave return to the previous pattern after five or six beats.

Although overdistension of the ventricle with impairment of nutrition of endocardial lamellae has been proposed as the explanation for T-wave changes following extrasystoles,[4] this is probably not the basis for the changes reported here. In these experiments basal extrasystoles caused a delay in repolarization in the area around the point of stimulation at the base, while apical extrasystoles produced a similar delay in the corresponding area at the apex. If ventricular distension were the cause, one would not expect such selective effects to appear, and the configurational changes would be the same regardless of the site of stimulation. Furthermore, since the hearts of these animals were presumably normal, the effects of overdistension should disappear after the first oncoming beat following the extrasystole rather than after the fourth or fifth beat. The presumption is justified that the change has been caused by an electrical effect at the point of application of the shock and in a sizeable area of myocardium around it.

The size of the area involved by the shock is the major portion, if not the entire area, of the proximal zone of the precordial lead. If only the point of stimulation were the seat of the alteration in repolarization, no significant changes would appear in the T waves of the oncoming beats following the extrasystole. Pinpoint currents of injury and pinpoint changes in repolarization caused by heating and cooling are not of sufficient magnitude to affect the precordial T wave. Furthermore, a pinpoint change in the distal zone would most certainly not be detectable in the precordial lead, since it has been shown that alteration in the distal zone must involve a considerable portion of it to produce a configurational change in the T wave.[6] In these experiments basal stimulation did produce transient changes in the apical lead in the postextrasystolic beats. The presumption is strong, therefore, that a shock applied to either the base or the apex of the left ventricle alters the repolarization of a zone of myocardium almost equivalent in size to the area of the proximal zone. It has already been established that this area is at least 2 to 3 cm. in diameter.[6]

The striking difference in the magnitude of effect upon the T wave of the postextrasystolic beats produced by apical as compared with basal stimulation may be explained by the relation of the size of the areas involved to the size of their respective zones. If the major portion or the entire area of the proximal zone is involved by a shock, the changes in the T wave will be more pronounced than if an area of the same size is affected in the distal zone, since the latter is very large in comparison to the proximal zone. Thus an effect in a distal area comparable in size to the proximal zone would produce relatively minor alterations. This was encountered in these experiments and is readily explained on the basis of the view that a precordial V lead results from the interference of electrical potentials generated in the proximal and distal zones of that lead.

Since the cylindrical electrode was inserted at random depth from one experiment to the next, the resulting extrasystoles must have arisen at various depths in the left ventricular wall. This variation made no difference in the character of the T-wave changes in the oncoming beats since apical stimulation, at whatever depth the electrode happened to be, produced inversion of the T wave and prolongation of the Q-T interval in the several beats following the extrasystole. This demonstrates in another way the finding previously described from this laboratory that endocardial and epicardial stimulation produced extrasystoles of the same configuration in a precordial lead.[7] There is, therefore, no support from these obser-

vations for the view that the T wave is the result of the interference between potentials generated at the endocardial and epicardial surfaces beneath the exploring electrode.

The final problem raised by these observations is whether the applied shock causing the extrasystole depolarizes a small point between the stimulating electrodes but affects the repolarization of a large area around it, or whether a threshold shock in the heart brings into activity not the muscle at the point of the electrodes alone but a much larger area, perhaps comparable with the area whose repolarization is affected in the succeeding beats. This question is important, since much electrocardiographic experimentation has depended on the assumption that a threshold shock depolarizes the area immediately around the stimulating electrode and that the propagated disturbance begins from this point. These experiments do not actually disprove this assumption, but they do cast some doubt upon it, since the shock affects a large area in the myocardium around the point of stimulation insofar as the repolarization process is concerned. The concept that the depolarization caused by a threshold shock in the ventricle begins at a point cannot be assumed and requires further experimentation. In this connection it is worth while to point out that Lewis did make this assumption when he proposed the theory of limited potential differences on the basis of a difference in appearance of endocardial and epicardial extrasystoles.[5]

Summary

A threshold rectangular wave shock applied to either the base or the apex of the left ventricle in situ was shown to produce an extrasystole and a delay in repolarization of an area around the stimulating electrode of about 2 to 3 cm. in diameter, which endured for four or five succeeding beats.

Sumario Español

Un estímulo de umbral aplicado al ápice o a la base del ventrículo canino intacto a cualquier profundidad del miocardio produce una demora en la repolarización durante las próximas tres o cuatro pulsaciones normales, en un área equivalente al tamaño de la zona próxima al terminal de la derivación precordial. Este cambio en repolarización no se debe a distensión postextrasistólica del ventrículo. El problema de que un estímulo de umbral inicia un disturbio propagado desde el punto del electrodo, o desde el área mayor cuya repolarización es alterada se discute.

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Atabrine in Ventricular Tachycardia

By Antonio M. Samia, M.D., and Mariano M. Alimurung, M.D.

The therapeutic efficacy of Atabrine in ventricular tachycardia has not yet been clearly demonstrated. In this case report, Atabrine stopped ventricular tachycardia and restored normal sinus rhythm following the fifth two-hourly oral dose of 0.30 Gm. Nausea and vomiting were the only toxic effects noted. Ventricular tachycardia, in this case, occurred as a complication of acute myocardial infarction. The latter's characteristic electrocardiographic picture became obvious as the arrhythmia was corrected.

IN RECENT YEARS several reports have been published indicating the therapeutic value of Atabrine for the correction of cardiac arrhythmias, particularly the supraventricular types. Very few cases of ventricular tachycardia have been treated with Atabrine and in none was a successful result obtained. The following case is therefore reported to point out the potentialities of Atabrine in ventricular tachycardia and to stimulate further studies with this drug in the ventricular arrhythmias.

Case Report

When first seen, A. G., a married Spanish male, 60 years of age, complained of "pain in the throat" which radiated to the epigastrium and was of approximately 24 hours' duration. The condition started suddenly while he was playing billiards after a heavy dinner. The pain was soon followed by palpitation, difficulty in breathing, nausea and vomiting.

Previous to this illness, the patient had had slight exertional dyspnea but never accompanied by any chest pain or discomfort. To his knowledge, his blood pressure had always been normal.

Physical examination revealed a markedly dyspneic, moderately cyanotic, anxious patient bathed in cold clammy perspiration. The pulse was imperceptible, the blood pressure unobtainable, and the heart sounds very faint and rapid. The electrocardiogram (fig. 1) revealed ventricular tachycardia at a rate of 200 per minute.

The patient was immediately placed under oxygen. Caffeine sodiobenzoate was given intramuscularly, 0.50 Gm. every three hours. The blood pressure was soon recorded at 110/80. Procaine amide, 200 mg., (Pronestyl) was next given intravenously under blood pressure and electrocardiographic control. During the Pronestyl administration the blood pressure fluctuated between 110/80 and 94/80, but the ventricular tachycardia persisted. Following the intravenous dose, Pronestyl was also given orally in a dose of 1.0 Gm. every two hours for two doses and afterward at six-hour intervals. In addition, 100 mg. of khellin (Kelicorin) was given intramuscularly once daily. The heart rate remained between 110 and 130 per minute and the blood pressure between 110/90 and 96/80.

On the second hospital day, 400 mg. of Pronestyl in 500 cc. of 5 per cent dextrose in water were given by slow venoclysis in addition to the oral doses. The arrhythmia still persisted as disclosed by the daily electrocardiograms. In two days the total dose of Pronestyl given was 11.6 Gm.

On the third day, quinidine sulfate (Quinicor) was given instead of Pronestyl in a dose of 0.40 Gm. every hour for three doses and then the same dose every three hours. Later, this was increased to 0.60 Gm. every three hours and finally every two hours. The pulse rate slowed down slightly to between 110 and 115, while the blood pressure fluctuated between 110/86 and 90/70. With a total dose of 5.6 Gm., the patient complained of tinnitus. The drug was finally discontinued when a total dose of 11.2 Gm. had been given in two and one-half days. The patient became nauseated and began to sweat profusely with consequent general weakness. He refused to take any more of the medicine. The pulse rate then rose to 140 and the blood pressure remained between 118/70 and 86/72. The serial electrocardiograms showed no change in the arrhythmia.

On the sixth hospital day, quinidine was stopped. Then, about four hours after the last dose of quinidine, the patient was started on Atabrine in a dose of 0.30 Gm. every two hours. When next seen, after five doses of Atabrine, the patient exhibited for the first time a pulse rate of 92 per minute. Similarly,

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the electrocardiogram disclosed the first instance of normal sinus rhythm with only occasional ectopic ventricular complexes. At the same time, the tracing finally revealed the underlying cardiac pathology, myocardial infarction of anteroposterior location with septal involvement (fig. 2). From then on, the pulse rate remained in a normal range, between 80 and 90, and the blood pressure remained between

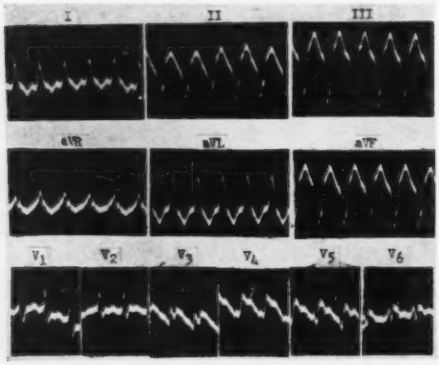

FIG. 1. Electrocardiograms of patient taken on the second day (first hospital day).

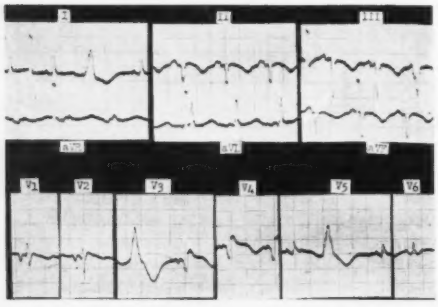

FIG. 2. Electrocardiograms of patient taken on the seventh hospital day.

112/86 and 90/60. Subsequent electrocardiograms showed the progressive changes resulting from the infarction, as well as the total disappearance of the ectopic rhythm. Two hours after the last dose of Atabrine, the patient vomited and then refused to take the next dose. The drug was, therefore, tapered off and discontinued after two additional days. During the rest of his stay in the hospital the patient improved steadily, in spite of a mild pneumonic process which was promptly checked with antibiotics. When discharged, after 39 days in the hospital, his electrocardiogram still showed the evidences of infarction but there was no trace of the ventricular tachycardia. The clinical course in relation to the cardiac arrhythmia and the drugs employed is illustrated in figure 3.

Two and one-half months later, the patient was re-examined. He stated that, since leaving the hospital, he continued to improve. He had had no chest pain. The heart rate was 82 per minute and the blood pressure was 140/96. The heart sounds were clear, regular and of good quality. The standing treatment consisted of Kelicorin, one tablet three times a day and one ampule once a week. The electrocardiogram then revealed some improvement in the S-T and T configuration in the extremity leads.

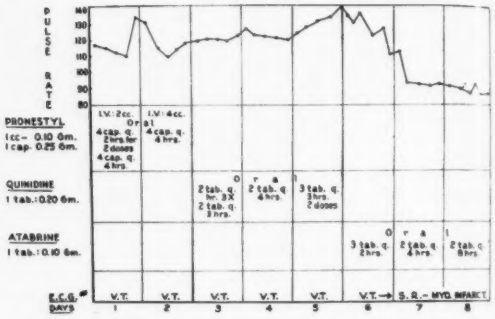

FIG. 3. Clinical course of patient in relation to the cardiac arrhythmia and the drugs employed.

* V. T. = Ventricular Tachycardia; S. R. = Sinus Rhythm.

DISCUSSION

In 1945 Babkin and Ritchie[1] demonstrated that quinine partially paralyzed the vagal inhibitory fibers of the dog's heart. Two years later, Gertler and Karp[2] observed that Atabrine possessed an identical property. This parallelism of pharmacologic effect and the established efficacy of quinidine, an isomer of quinine, in restoring regular sinus rhythm to hearts in auricular fibrillation and other cardiac arrhythmias suggested that Atabrine would be similarly effective. This hypothesis was soon verified in experimentally produced arrhythmias in dogs by Gertler and Karp[3] as well as in clinical trials on hospitalized patients by Gertler and Yohalem.[4]

Following closely these initial encouraging clinical results, Vega Diaz[5] in 1948 reported a small series of six patients, four with paroxysmal auricular fibrillation, one with paroxysmal nodal tachycardia and one with paroxysmal

auricular flutter. In four of the six patients, the author obtained very spectacular results with the return to sinus rhythm occurring in from 20 seconds to 10 minutes following the intravenous or intramuscular administration of Atabrine.

In 1949 Gertler and Yohalem[6] reported a more extensive study on 26 patients with auricular fibrillation, two with nodal tachycardia, two with auricular flutter, and two with ventricular tachycardia. In those with auricular fibrillation, Atabrine gave successful results in 13 of 27 trials. Of added interest was the fact that quinidine, administered before Atabrine was given, was ineffective in 16 trials. Moreover quinidine and/or digitalis failed also in those patients in whom Atabrine, too, failed to restore a normal rhythm. In the other six cases with arrhythmias other than auricular fibrillation, Atabrine yielded successful results in three. The remaining unsuccessful ones included the two cases of ventricular tachycardia.

These authors concluded that the best results with Atabrine seemed to occur in older patients with arteriosclerotic heart disease and in younger patients in whom the arrhythmia was of less than 48 hours duration. The time of disappearance of the arrhythmias occurred at the time when the maximum blood levels of Atabrine had been reached following intramuscular injections of the drug. The only toxic effects noted were nausea and vomiting.

It would seem, therefore, that our single case of ventricular tachycardia treated with Atabrine, while not the first case so treated, could very well be the first reported case in which successful results were obtained with Atabrine in this type of arrhythmia. The literature would readily suggest that the therapeutic use of Atabrine as an antiarrhythmic should perhaps be limited to supraventricular arrhythmias. Nevertheless, the fact that we failed to restore normal sinus rhythm with more than adequate doses of Pronestyl first and quinidine later presented a situation in which we were forced to try any other known antiarrhythmic measure. Unlike the cases previously reported, Atabrine was administered orally rather than parenterally; however, the dose at which reversion to sinus rhythm occurred paralleled closely that which other authors found to be therapeutically effective.

The conclusion that Atabrine was responsible for the correction of the arrhythmia in this case seems very reasonable because such correction occurred at the time when the desired blood concentration must have been reached. That Pronestyl was not the effective measure in the control of the arrhythmia is very obvious. That control was not due to quinidine is also quite evident for two main reasons: First, the arrhythmia persisted in spite of clinical signs of quinidine toxicity; second, the reversal to sinus rhythm occurred not at the time when the plasma quinidine concentration was highest[7] but rather about 16 hours after the last dose of quinidine.

This case also corroborates the observations of others regarding the lack of serious toxic effects of Atabrine even with such high doses as were given. Similarly, nausea and vomiting were the only side effects produced.

Incidentally our experience in this case further demonstrates the value of serial electrocardiograms not only for the study of the arrhythmia but for the disclosure of the underlying cardiac pathology. The electrocardiographic alterations of the latter may be significantly masked by the complicating arrhythmia, especially in ventricular tachycardia. The latter produces so much distortion in the ventricular complexes that most other conditions may not be sufficiently exhibited in the tracing. As soon as the normal mechanism is reestablished following correction of the ventricular tachycardia, the electrocardiographic features of myocardial infarction become evident.

Considering the gravity of ventricular tachycardia as a complicating arrhythmia in myocardial infarction and the success obtained in this case with Atabrine, after vain attempts with Pronestyl and quinidine, this single experience should reawaken interest in further studies on Atabrine in ventricular tachycardia. While this report is not intended to indicate that Atabrine is superior to either Pronestyl or quinidine, it nevertheless adds additional clinical evidence of the antiarrhythmic properties

of Atabrine not only in supraventricular arrhythmias, but in ventricular tachycardia as well.

Summary

The abolition by Atabrine of ventricular tachycardia in a 60 year old male patient is reported. Atabrine restored normal sinus rhythm after Pronestyl and quinidine failed to do so.

Atabrine was given orally in doses of 0.30 Gm. every two hours. Reversal to sinus rhythm was noted after the fifth dose. The only toxic effects produced were nausea and vomiting, which occurred once following the fifth dose.

The underlying disease, myocardial infarction, became obvious as sinus rhythm was restored. This illustrates the value of serial electrocardiographic studies particularly in the presence of ventricular tachycardia which in this case masked the electrocardiographic features of myocardial infarction.

Sumario Español

La eficacia terapéutica de la atabrina en la taquicardia ventricular no se ha podido demostrar aún claramente. En este informe de un caso, la atabrina terminó una taquicardia ventricular restaurando un ritmo sinuauricular luego de la quinta dosis a intervalos de dos horas de 0.30 Gm. Los únicos efectos tóxicos observados fueron nausea y vómitos.

La taquicardia ventricular en este caso ocurrió como complicación de un infarto agudo del miocardio. Los hallazgos característicos de infarto agudo se mostraron obvios cuando se terminó la arritmia.

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The Spatial Orientation of the Plane Including the Mean QRS and T Vector of the Normal Electrocardiogram

By NOBORU KIMURA, M.D., PH.D.

For measurement of the spatial orientation of planes in the analysis of the spatial vectorcardiogram, a simple device is developed to be used with Simonson's vector analyzer for the conventional electrocardiogram. The prospective value of this method is shown for the measurement of the plane including the mean QRS and T vector.

THERE is some evidence[1, 2] that the spatial angle between the mean QRS and T vector might serve as an important criterion for the diagnosis of ventricular hypertrophy or coronary insufficiency, although the angle was not actually measured. Recently, a method has been described[3] to construct and measure this angle from the conventional electrocardiogram. With this method, a vector is defined in terms of its direction in the horizontal plane (H°), its vertical angle (V°, elevation), and its magnitude. The method is simple; the measurement of a vector can be completed within three minutes or less.

For some purposes, at least, it may be desirable to analyze not only the spatial angle between the mean QRS and T vector, but also the spatial orientation of the plane included by these vectors. The present report indicates the findings in exploratory studies.

METHOD

The spatial orientation of a plane can be measured in terms of the spatial position of a vertical projection on that plane. Using vector analysis for the determination, the vertical projection must pass through the center (C) of the sphere (S, fig. 1) which is the theoretic electrical center of the heart.

The auxiliary equipment for measurement of the orientation of planes and its operation is shown in figures 1 and 2. It consists of a transparent triangle "T," with a semicircle "Y" of a radius of 1.25 inches to fit the surface of the sphere "S," and a bent metallic rod "E." The projection of E passes through the center C. Figure 1 shows the first two steps of the operation. Vector rod A_1 is the mean QRS vector, and A_2 is the mean T vector. The transparent triangle is placed on A_1 and A_2 and thus shows the plane included by the mean QRS and T vector. The prolongation of rod E passes through the center and thus defines the orientation of that plane. Vector rod A_3 is now slid on the surface of S parallel to E.

The triangle T, and rods A_1 and A_2 can now be removed, and the spatial orientation of A_3 measured (fig. 2). The measurement of the vertical angle V is identical with the procedure described before: the distance between the ends of A_3 and the rod (O) in the center of the horizontal plane is measured with a special straight ruler, converting the distance into angles. For measurement of the horizontal angle (H°), the moveable vector rod P is put in contact with A_3, and the rectangular ruler "U" on the horizontal plane is moved to contact with P (fig. 2). The horizontal angle is now read at the edge of the ruler on the circular scale (left forefinger). The whole procedure of measurement of the spatial orientation of a plane can be done within approximately one minute.

RESULTS AND DISCUSSION

Table 1 shows the means and standard deviations of the spatial mean QRS and T vectors of 44 normal men and in the last two columns the mean spatial orientation of the plane including these two vectors. In all normal persons, the plane is oriented posteriorly and upward.

For comparison, table 1 shows the values in six patients with various abnormalities. Patients Flo and Koch had left ventricular strain pattern (S-T depression and T inversion) in lead I and in V_6 (Flo), and in lead I and in

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This investigation was supported (in part) by a grant from the Minnesota Heart Association.

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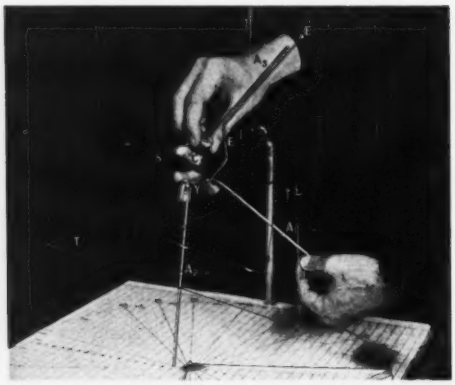

FIG. 1. Determination of spatial orientation of plane including the mean QRS and T vector. Step 1: Placing triangle on vectors A_1 and A_2. Step 2: Moving vector rod A_3 parallel to E.

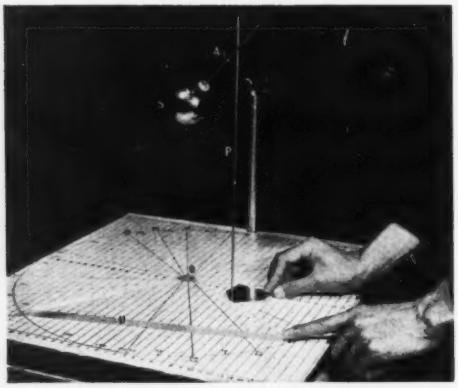

FIG. 2. Steps 3 and 4: Measuring of V° and H° of A_3.

leads V_4 to V_6 (Koch). Patient Mat had typical left bundle branch block in lead I and V_6. Patients Lyo and Slo had an abnormal Q with T inversion in lead I and V_3 to V_6 (Lyo), or V and V_6 (Slo). In patient Slo the R wave was absent in V_2 to V_4 (anterior-lateral infarct). In patient Cla, an abnormal Q wave was present in lead III and V_6, with mainly negative QRS deflection and T inversion in leads I, II and V (posterior-lateral myocardial infarct).

Among other abnormal characteristics of the spatial mean QRS and T vectors, the orientation of the plane defined by these vectors is very different from that of the normal group. The horizontal angle of the projection on that plane points anteriorly instead of posteriorly; the plane is tilted anteriorly instead of posteriorly. In both patients with anterior-lateral myocardial infarct the vertical angle of the projection (last column) is definitely lower; this means that the plane is nearly vertical.

It appears that the determination of the spatial orientation of this plane adds to the precise differentiation between normal and abnormal electrocardiograms.

SUMMARY

A method is described for measuring the spatial orientation of the plane included by the mean QRS and T vectors, by means of Simonson's spatial vector-analyzer. The spatial orientation of a plane is determined by the horizontal (H) and vertical (V) angle of its perpendicular, central projection. Values of

TABLE 1.—*Horizontal (H°), Vertical (V°) Angles and Magnitude (Mag), of Mean Spatial QRS and T Vectors; Spatial Orientation of the Plane Including these Vectors, Separated by the Angle dA°, in 44 Normal Men (Means) and Six Patients**

Subjects	Category	QRS			T			QRS-T Plane		
		H	V	Mag.	H	V	Mag.	dA	H	V
44	Normal Means	−23.6	46.3	10.5	+37.9	64.3	3.3	+49.8	−21	+136
Flo	L. Ventr. Strain	−44	117	24.8	+170	77	4.7	+147	+103	+150
Koc	L. Ventr. Strain	−65	93	21.0	+100	47	2.7	+108	+25.5	+106
Mat	L.B.B.B.	−63	108	25.0	+120	89	4.5	+93	+32	+106
Lyo	Ant. Infarct	−15	38	18.8	+171	83	1.7	+120	+80	+85
Slo	Ant. Infarct	−51	37	7.4	+124	125	2.2	+126	+35	+92
Cla	Post. Infarct	+130	113	7.6	+124	90	2.3	−23	+34	+105

* The normal and abnormal material is identical with that in reference 3.

patients with various lesions show marked differences in the spatial orientation of the plane included by the mean QRS and T vectors, compared to a group of 44 normal men.

Sumario Español

Para la medida de la orientación espacial de planos en el analisis del vectorcardiograma espacial, un artefacto sencillo se ha desarrollado para usarse con el analizador de vectores de Simonson para el electrocardiograma convencional. El valor anticipado de este método se demuestra para la medida del plano incluyendo el QRS promedio y el vector T.

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The Circulatory Response to the Valsalva Maneuver of Patients with Mitral Stenosis with and without Autonomic Blockade

By David G. Greene, M.D., and Ivan L. Bunnell, M.D.

Patients with clinically significant mitral stenosis have been demonstrated to differ from other subjects in their circulatory responses to the Valsalva maneuver. During forced expiration most patients with mitral stenosis are able to maintain systolic pressure in the brachial artery at a level equal to or greater than the resting value, whereas most control subjects cannot. Autonomic blockade does not affect the ability of patients with mitral stenosis to maintain systolic pressure, whereas it abolishes such ability, when it is present, in control subjects. The unique response of patients with mitral stenosis under autonomic blockade is attributed to the physiologic consequences of the volume of blood in the dilated left atrium.

INTERPRETATION OF hemodynamic data may be facilitated by comparison of observations made before and after autonomic blockade. The present study is based upon the circulatory responses to the Valsalva maneuver of patients with mitral stenosis. Analysis of the brachial arterial pressure pulses obtained during the maneuver reveals that the responses of patients with mitral stenosis differ from those of other patients, and that the differences are accentuated under autonomic blockade.

Method

Fifty-four patients* have been studied, among whom were 20 with rheumatic heart disease; these 20 have been classified as to clinical status and valvular involvement on the basis of history and physical examination, fluoroscopic and electrocardiographic interpretation, cardiac catheterization and the findings at surgery, when performed. Fifteen of the 20 patients were catheterized and nine underwent valvuloplasty. Three patients were discovered to have a predominantly aortic valvular lesion and 17 were discovered to have mitral disease predominantly. Of the 17 patients with mitral disease 15 have been classified as having predominantly mitral stenosis and two as having predominantly mitral insufficiency. These 17 patients have been further divided according to clinical status. All were disabled by their disease; 13 were clinically progressive, while four were stable. The data on three of the patients with mitral stenosis were obtained postoperatively. One of the three had developed a marked degree of mitral insufficiency as a result of valvuloplasty.

The control group is composed of 39 individuals. The group is heterogeneous. It includes patients with and without heart disease, as well as subjects with no known disease. The patients classified as having aortic valvular lesions or mitral insufficiency have been included among the controls for the purposes of this study, since their responses followed the normal pattern.

An indwelling needle was placed in the brachial artery and the blood pressure recorded through a Hathaway pressure recording system.[1] A mouthpiece was inserted to which were connected an aneroid manometer and a pressure gage which recorded mouth pressure graphically. The subject was instructed to blow the indicator needle of the aneroid manometer to about the 40 mm. mark for 15 seconds. Whenever feasible, the same procedure was followed after autonomic blockade. Blockade was achieved by intravenous infusion of tetraethylammonium chloride at rates of 0.22 to 0.79 mg. per kilogram per minute. Records analyzed include those recorded after 6 to 50 minutes of continuous intravenous infusion at the above rates.[4]

Each subject performed more than one Valsalva maneuver. The particular record selected for tabulation was the one which was best performed, that is, in which the forced expiration was performed evenly for the full 15 seconds, and which produced a circulatory response typical for that particular patient, as judged from analysis of each of his records. Not all patients were able to achieve a mouth pressure of

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This study was supported by a grant from the Masonic Foundation for Medical Research and Human Welfare.

* The data from some of these studies have been previously reported.[4]

40 mm. Hg. The absolute level attained did not appear to affect the type of circulatory response.

This communication will be concerned with measurements of systolic and pulse pressures and heart rate, at three points (A, B, C) in each record (fig. 1). Point A is two complete respirations during the resting period, before any forced expiration has occurred. Point B is selected as the last few beats during the period of forced expiration. Point C is represented by the second and third respirations following the cessation of forced expiration.

Results

Description of the contrasting circulatory responses of the two groups to forced expiration will be arbitrarily limited to the levels of brachial artery pressure and heart rate at points

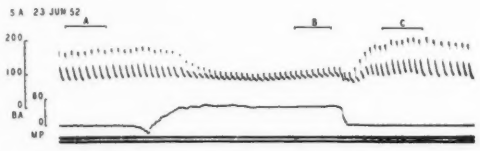

Fig. 1. Normal response to the Valsalva maneuver. Point A is two complete respirations at rest, before the expiratory effort. Point B is the last few beats before the end of forced expiration. Point C is the second and third respirations following the end of forced expiration. Systolic pressure at point B is lower than at point A. There is an overshoot at point C. In this and subsequent figures, the upper curve represents brachial arterial pressure, the lower curve mouth pressure as measured at the mouthpiece, and the other line or lines are base lines. Scales are in millimeters of mercury.

B and C during the Valsalva maneuver. The response of the controls will be considered first. Figure 1 exemplifies the commonest response seen among the controls. Either with the onset of forced expiration, or shortly thereafter, systolic pressure falls below the resting value. At point B, near the end of the period of forced expiration, the majority of the controls (64 per cent) had a systolic pressure lower than the resting value, point A (table 1). The remaining 36 per cent of controls had either maintained or regained their resting systolic pressure at point B; this rise in pressure was, in some instances, a late phenomenon (fig. 2) occurring during the latter half of forced expiration, at a time when all but one of the subjects exhibited a tachycardia. All but one control subject showed a reduced pulse pressure during this period of forced expiration.

After forced expiration was ended, and the first breath was taken, brachial artery pressure fell abruptly. This was followed by a rapid rise until during the second and third respirations, point C, the systolic pressure rose above the resting value (figs. 1 and 2). This constitutes the "overshoot" phenomenon, and was seen in

Table 1.—*Systolic Pressure at End of Forced Expiration*

	Number of Subjects			
	Without TEAC		With TEAC*	
	Col. 1 Equal to or Greater than Resting Value	Col. 2 Less than Resting Value	Col. 3 Equal to or Greater than Resting Value	Col. 4 Less than Resting Value
Controls				
Random Patients	13	21	0	5
Aortic Lesion	1	2	0	1
Mitral Insufficiency	0	2	0	0
Total	14	25	0	6
Mitral Stenosis	13	2	6	0

* Only certain of those subjects in column 1 received TEAC. Columns 3 and 4 include only subjects who originally were placed in column 1.

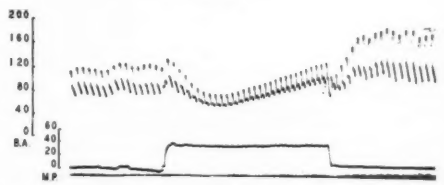

Fig. 2. Normal response to the Valsalva maneuver. Systolic pressure rises above the resting level before the end of the forced expiration, and there is an overshoot.

79 per cent of control subjects (table 2). During the second and third respirations, the heart rate usually slowed. However, in 17 of 32 controls in which an accurate measure of heart rate was obtainable, it did not fall below the resting value.

Figure 3 exemplifies the circulatory response of patients with mitral stenosis to the Valsalva maneuver. As can be seen from table 1, most of

the test group (13 out of 15 subjects or 87 per cent) have a systolic pressure at the end of forced expiration equal to or greater than the resting level. At the same time, the pulse pressure was increased in 6 out of the 15 subjects. During the second and third respirations after forced expiration was terminated, 11 of 15 subjects (73 per cent) exhibited a systolic overshoot. (See table 2.) It is difficult to make any statement about heart rate in the records obtained in mitral stenosis since more than half the subjects (8 out of 15) exhibited atrial fibrillation. Of those with regular sinus rhythm,

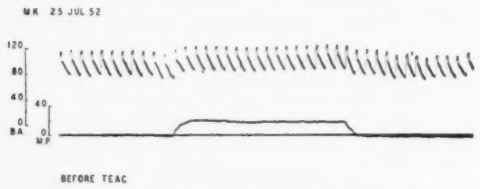

FIG. 3. Response of patient with mitral stenosis to the Valsalva maneuver. Systolic pressure is maintained throughout the period of forced expiration, and in this instance there is no overshoot.

TABLE 2.—*The Occurrence of Systolic Overshoot and Bradycardia during the Second and Third Respirations after Forced Expiration*

	Systolic Overshoot		Bradycardia*	
	Present	Absent	Present	Absent
Controls	31	8	16	17
Mitral Stenosis	11	4	1	6

* Includes only those patients with regular sinus rhythm, whose records could be accurately timed.

only one out of seven showed a heart rate at point C slower than at point A.

After autonomic blockade had been achieved by the administration of tetraethylammonium chloride (TEAC), subjects in both groups showed generally lower systemic arterial pressure. All 19 members of the control group who had received tetraethylammonium chloride failed to demonstrate an overshoot. Of the 14 controls that had been able, before autonomic blockade, to regain resting systolic pressures at point B, six received the blocking agent tetraethylammonium chloride. All six lost this ability to regain resting systolic pressure during forced expiration (fig. 4). Six subjects with mitral stenosis received tetraethylammonium chloride. All now failed to show an overshoot. Each had previously maintained systolic pressure during forced expiration, and now despite the action of the blocking agent, all six retained this ability (fig. 5).

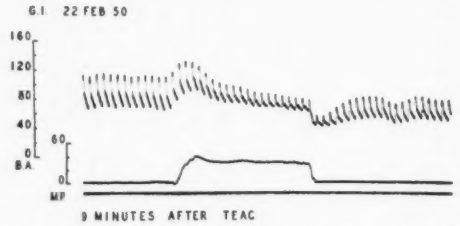

FIG. 4. Response of control patient to the Valsalva maneuver during autonomic blockade. Systolic pressure does not regain resting level, and there is no overshoot.

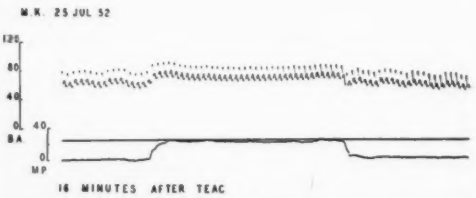

FIG. 5. Response of patient with mitral stenosis to the Valsalva maneuver during autonomic blockade. Although the blood pressure level is lower, the form of the tracing is similar to that of the same patient before autonomic blockade taken a few minutes earlier (fig. 3). Systolic pressure is maintained throughout the period of forced expiration.

DISCUSSION

The classic circulatory response to the Valsalva maneuver has been well described.[2, 3, 4] The responses of the control group, both with regard to brachial artery pressure and heart rate, are consistent with the accepted normal responses. Some normals are able to maintain or regain resting systolic pressure during expiratory pressure, while others are unable to do so. The elevated systolic pressure late in the period of forced expiration was accompanied by tachycardia, suggesting that both are of reflex origin.[2, 4] This concept is further supported by the fact that in each instance in

which it was achieved, autonomic blockade abolished this ability to maintain or regain resting systolic pressure.

Most patients with mitral stenosis, on the other hand, would appear to be able to maintain systolic pressure without regard to reflex mechanisms. This is suggested by the fact that their systolic pressure at the end of forced expiration was equal to or greater than the resting value, whether or not autonomic blockade was induced. One is led to the conclusion that there is, in mitral stenosis, a mechanical reason for systolic pressure maintenance during forced expiration. In the control subject, forced expiration leads to increased intrathoracic pressure and a consequent reduction in venous return to the right atrium. After the first few beats, the venous return to the left atrium is also reduced, as is left ventricular filling. Without the compensatory reflex effect of tachycardia and peripheral arteriolar vasoconstriction, the reduced left ventricular filling and output inevitably lead to a fall in systemic arterial pressure as forced expiration is prolonged. In mitral stenosis, there is a large reservoir of blood in the dilated left atrium, which, trapped behind a stenotic orifice, can maintain good left ventricular filling during the 15 seconds of forced expiration. This ensures maintenance of left ventricular output and, with it, maintenance of systemic artery pressure, wholly apart from the effect of any reflexes.

It is only in the above regard that the control and mitral stenosis groups are clearly differentiated in their response. An overshoot was present in 79 per cent of control Valsalva maneuvers, and in only slightly fewer of the mitral group, 73 per cent. Tetraethylammonium chloride infusion abolished the overshoot in all subjects who received the drug in each group. Comparison of the test and control groups with regard to changes in heart rate after forced expiration is ended is obscured by two facts: (a) that more than half the test group were fibrillating, and (b) the control group shows no consistency of pattern with regard to heart rate. So although six of the seven patients with mitral stenosis with regular rhythm do not show a bradycardia at point C, neither do half the controls.

Recently Goldberg, Elisberg, and Katz[5] have studied the circulatory responses to the Valsalva maneuver of clinically significant mitral stenosis, and have concluded that it differs from only acoustically significant mitral stenosis, and normalcy, in two regards. These are the lack of (a) the overshoot and (b) the bradycardia which normally accompanies it. The authors suggest that it may be possible to utilize the latter as a simple bedside test for clinically significant mitral stenosis. From our observations, neither of these criteria would appear to be critical in the evaluation of mitral stenosis.

In our particular series of subjects with mitral stenosis, all had lesions of sufficiently high grade to be of clinical significance. We can therefore say nothing about the circulatory response of only acoustically significant mitral stenosis.

Summary

Only patients with clinically significant mitral stenosis were able to maintain systolic pressure in a systemic artery during the forced expiratory phase of the Valsalva maneuver when performed under effective autonomic blockade. Resting systolic pressure was regained in certain other subjects during forced expiration when the autonomic nervous system was functionally intact, but this was not observed after blockade. The unique response of patients with mitral stenosis is attributed to the physiologic consequence of the volume of blood in the dilated left atrium.

Sumario Español

Ha sido demostrado que pacientes con estenosis mitral clínicamente significativa difieren de otros sujetos en el respondimiento circulatorio a la maniobra de Valsalva. Durante la expiración forzada la mayoría de los pacientes con estenosis mitral pueden mantener una presión sistólica en la arteria braquial a un nivel igual o mayor que los valores obtenidos durante reposo, mientras que la mayoría de los sujetos controles no pudieron mantener la presión a este nivel. Bloqueo autonómico no afecta la abilidad de los pacientes con estenosis mitral a mantener la presión sistólica, pero

si abole esta abilidad cuando se encuentra presente en sujetos controles. El respondimiento único en pacientes con estenosis mitral bajo bloqueo autonómico se atribuye a los resultados fisiológicos del volumen de sangre en el aurículo izquierdo dilatado.

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The Kinetocardiogram

I. Method of Recording Precordial Movements

By E. E. Eddleman, Jr., M.D., Kathryn Willis, M.D., T. J. Reeves, M.D., and T. R. Harrison, M.D.

A simple method of recording low-frequency precordial movements is presented and termed kinetocardiogram to indicate movements as the result of the motions of the heart. The normal precordial patterns are described as well as the time relationships to the cardiac cycle and ballistocardiogram.

STUDIES of the graphic representation of the apex beat are well known[1, 2, 3, 4]; however, they have not been widely used clinically. Recently, Johnston and Overy[5] revived interest in low-frequency precordial vibrations with a review of the literature and a presentation of a few records obtained from normal and abnormal subjects. They employed an electromanometer with a pickup device that is maintained airtight against the chest. Luisada and Magri[6] presented a series of similar low-frequency tracings obtained by use of a crystal microphone.

The present communication presents a simple method by which the movements of the chest wall can be recorded, and also deals with the general pattern of records obtained from young normal individuals.

Methods

The pickup device employed is a metal bellows that transforms chest wall movements into a pulse wave in an airtight system, which in turn is transformed by a piezoelectric transducer* into an electric current. Almost any type of electrocardiographic apparatus can be used as a recorder. Figure 1 is a diagram of the apparatus. Attached to the bellows is a small metal arm approximately 1½ inches long, which has a flat endpiece 7 mm. in diameter that is placed against the chest wall. The bellows itself is approximately 2 inches in diameter, consists of two flanges, and is connected by a thick-walled rubber tubing to the piezoelectric transducer (fig. 1). Several other types of bellows were tested and, in general, were satisfactory, so that the dimension of the one used for this study is not necessarily essential. However, one should use a bellows with a relatively high degree of sensitivity, since the motions over the chest wall usually range from 5 microns in the left axilla up to 200 microns directly over the precordium. The bellows pickup, as described, responds to pure displacement of the inward and outward motions of the chest on the spot where the pickup arm is placed. Records are obtained during held end of normal expiration, thus eliminating respiratory movements. Over a wide range of motions these recordings proved to be linear in character, by comparison to a sine wave of known amplitude and frequency. Records of frequencies from 0.8 to 5 vibrations per second have been artificially produced with a fair degree of accuracy, and without appreciable fall in response. The lag in the system was found to be negligible, or less than 0.005 second. The pickup arm of the bellows is placed firmly against the chest; however, the degree of pressure need not be kept constant. Better records are obtained if the pickup is not placed on a rib, but this again is not necessarily essential. The entire bellows and pickup piece can usually be mounted on a crossbar, and, with the use of a universal-type clamp, the endpiece can easily be applied perpendicular to any place on the chest from which displacement records are desired. The recording equipment used in this study is the Cambridge 4-channel direct writer.

Procedure

Records were obtained in positions on the chest wall which corresponded to the conventional precordial electrocardiographic leads, V_1 through V_6. These were chosen, since they are related to known chest landmarks, and because they are over the basilar, mid, and apical regions of the ventricles. The terms KV_1, etc., are used to avoid confusion with the precordial electrocardiographic terminology, and to designate the same location on the chest wall. Simultaneous heart sounds, carotid pulse, and

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This investigation was supported by a research grant H-959(C) from the National Heart Institute, of the National Institutes of Health, Public Health Service.

* Commercially available from the Cambridge Company, Ossining, New York.

displacement ballistocardiograms[7] were obtained. Records were made on normal male adults of ages between 20 and 30 years.

Calibration

A special apparatus was constructed that consists of a motor-driven eccentric, which moves a bar back and forth through a known distance in a manner to produce a sine wave.* Thus, by comparing the amplitude response from the sine wave generator, and

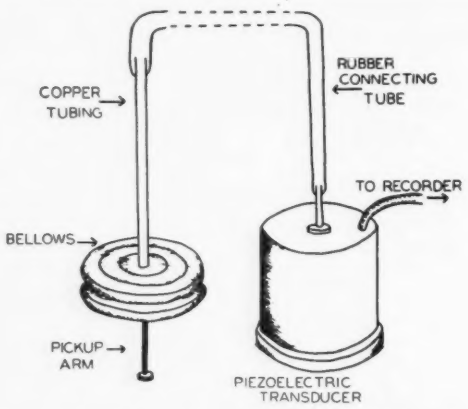

FIG. 1. A diagram of the apparatus used to record the precordial pulsations. A small metal arm 1½ inches long, with a flat endpiece 7 mm. in diameter contacting the chest wall, transmits the chest motion to the bellows. The bellows has two flanges about 2 inches in diameter, with two circumferential corrugations. The endpiece is placed against the chest wall perpendicular to the spot where records are desired. The bellows transfers the movements into a pulse wave in the airtight system, which is connected by means of rubber tubing to the piezoelectric transducer. The output from the piezoelectric transducer may be recorded on any standard recording apparatus. The bellows and pickup arm may be mounted on a crossbar suspended over the patient, and with the use of a universal clamp on the copper tubing records can be obtained from any place on the chest wall.

the amplitude of the records produced on the chest wall, a direct estimation of the magnitude of the precordial pulsations could be made. From this it was determined that the amplitude of the precordial motions were from about one to 200 microns, depending on the location on the chest from which the record was obtained, and the physical characteristics of the chest wall. Thus standardization is possible at different times, as well as in different individuals.

* Constructed by The Turkey Creek Manufacturing Company, Birmingham, Ala.

RESULTS

Figures 2*A* and *B* are records of two normal subjects. Systole and diastole are delineated in one cycle of each record. Note the similarity of patterns from records obtained from comparable positions on the chest in different subjects. Figure 3 is a record obtained from one normal subject with simultaneous heart sounds, carotid pulses, and displacement ballistocardiogram. The demarcation of the phases of the cardiac cycle is slightly modified from that described by Wiggers.[8] Ejection was assumed to begin 0.02 second before the upswing noted on the carotid pulse.* The characteristic pattern of these precordial movements may be analyzed in some detail in relation to the various phases of the cardiac cycle.

Protosystole† or Early Isometric Contraction

Figure 3 is a detailed record of KV_1 through KV_6, while figure 4 is a composite diagram of KV_1 and KV_4. Both figures can be used to refer to this phase, as well as the subsequent phases in the preceding paragraph. About 0.04 second before the first heart sound, and approximately with the onset of Q in the electrocardiogram, an outward motion is noted over the base of the ventricles (KV_1 through KV_3), and may occasionally be noted as far over as the apex. This outward motion is present in subjects with auricular fibrillation and complete heart block. Thus it apparently represents some ventricular activity taking place before the closure of the atrioventricular valves.

Late Isometric Contraction

The outward movement which begins in protosystole continues into isometric contrac-

* It is realized that the time lag of the pulse wave from the aorta to the carotid is not always 0.02 second; however, 0.02 second was chosen as an average transmission time. The time value probably varies somewhat from 0.01 to 0.03 second.

† The term "protosystole" is used to denote the brief period between what appears to be the onset of ventricular systole and the closure of the auriculoventricular valves. Its duration is approximately 0.03 second. The term "late isometric contraction," denotes the period between the beginning of the first heart sound and the onset of ejection.

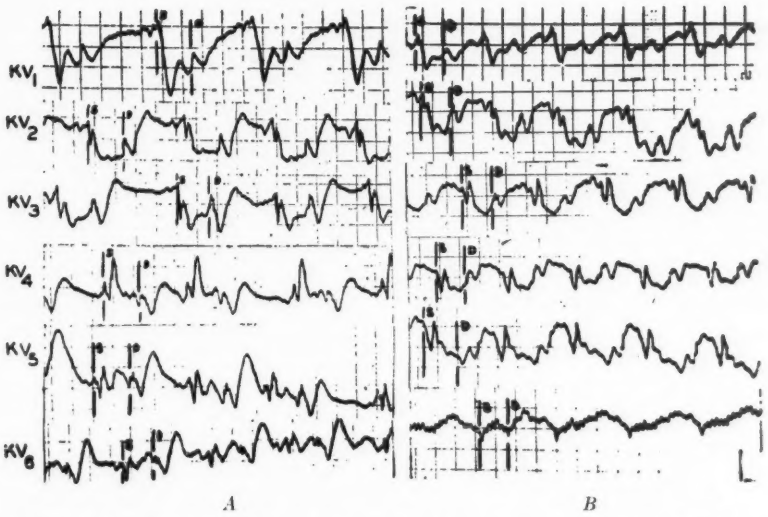

FIG. 2*A* and *B*. Records obtained from two normal subjects. Systole, as indicated by "S," and diastole, as indicated by "D," are indicated in one of the cycles for orientation purposes. An upward motion indicates an outward movement of the chest, while a downward motion indicates an inward motion of the chest wall. Note the similarity of records obtained in comparable positions on the chest, while there is some dissimilarity between records obtained in the different positions on the chest wall. In figure *A*, note the marked outward movement occurring just after the beginning of systole in KV_4. This is probably the graphic representation of the apical thrust.

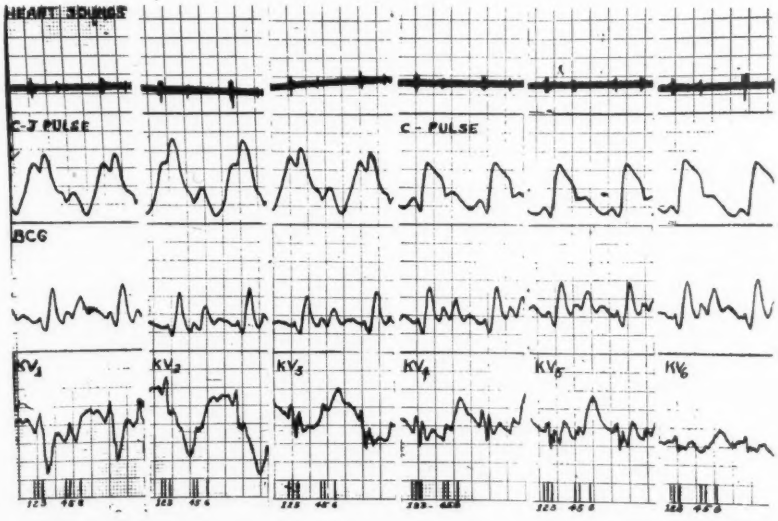

FIG. 3. The records are obtained from positions KV_1 through KV_6 in a normal individual, with simultaneous carotojugular and carotid pulse, heart sounds, and displacement ballistocardiograms. The phases of the cardiac cycle are demarcated below by a short line, numbers 1 through 6. The phase from 1 to 2 represents protosystole; from 2 to 3 late isometric contraction; from 3 to 4 ejection systole; from 4 to 5 protodiastole; and from 5 to 6 isometric diastole. Note that records obtained from KV_2 and KV_3 are somewhat intermediate in pattern from those of KV_1 and KV_4.

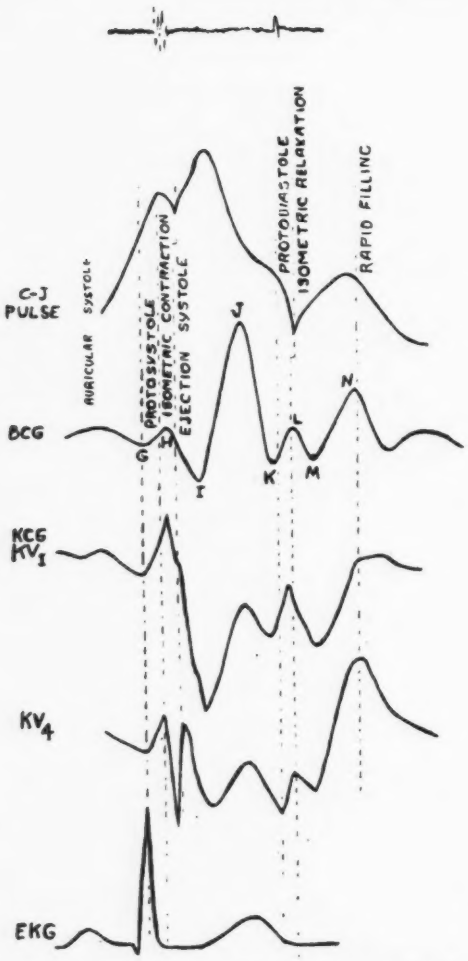

FIG. 4. This represents a composite diagram of the records obtained from KV_1 and KV_4, as compared with the heart sounds, a carotojugular pulse, displacement ballistocardiogram, and electrocardiograms (lead II). Note that in KV_1 there is an outward motion occurring almost simultaneously with the peak of the P wave, which probably is the result of auricular contraction. An outward movement begins approximately 0.04 second before the first heart sound, during the period which has been designated as protosystole. The outward movement, which begins in protosystole in KV_1, continues almost to late isometric contraction, and roughly parallels the GH upstroke on the ballistocardiogram. Almost simultaneous with the first heart sound, there is an inward motion noted in KV_4, followed quickly by an outward movement which is probably the apical thrust. By the beginning of ejection systole, both apical and basal regions of the heart are moving inward. A slow outward motion is noted in midsystole, which corresponds to the IJ upstroke, reaching a peak approximately at the same time as the J, and subsequently subsiding, paralleling the JK downstroke on the ballistocardiogram. This is noted most frequently in KV_1. However, in this instance it is noted as far away as KV_4. In both KV_4 and KV_1 there is noted a sharp upstroke just before protodiastole and paralleling the KL upstroke on the ballistocardiogram. This is followed by an inward motion, usually most prominently noted in KV_4. However, it may be present over both the apical and the basilar regions of the heart. During isometric relaxation there is a marked outward motion noted in both apical and basilar regions of the ventricles, which may parallel the MN upstroke on the ballistocardiogram.

tion (in KV_1 and sometimes in KV_2), and may parallel the GH upstroke of the ballistocardiogram. A quick inward motion in KV_3 through KV_5 and sometimes KV_6, occurs almost synchronously with the first heart sound, or approximately 0.01 to 0.02 second following it. This inward motion does not necessarily start at the same time in the various positions, and occurs too soon after the first heart sound to indicate the beginning of ejection. This inward motion is followed by a marked outward movement, most prominent in KV_4 or at the apical region. However, it may be present over the base of the heart (KV_2), or as far out as KV_6. This outward movement is probably a graphic representation of the apical thrust. Usually, an inward motion is noted in KV_1 at the same time the outward motion occurs in KV_4, which may be synchronous with the beginning of the H-I downstroke in the ballistocardiogram.

Ejection Systole

Approximately 0.02 second before the carotid upstroke there is a general inward motion noted from KV_1 to KV_5, and often as far out as KV_6, as ventricular ejection occurs. It was noted that this inward motion does not occur simultaneously in all positions and, in general, was 0.02 second earlier in KV_2 and KV_3 than in KV_4. Following this inward motion, during ejection, there occurs a relatively slow outward motion in midsystole, most prominent in KV_1, and occasionally in KV_2, and seldom noted as far over as KV_3. The onset of this slow out-

ward motion is usually simultaneous with the IJ upstroke in the ballistocardiogram, and its peak is reached approximately at the same time as the J peak. Usually, this is followed by an inward motion corresponding to the JK downstroke in the ballistocardiogram.

Protodiastole

Approximately 0.01 to 0.02 second before or after the second heart sound, there occurs a sharp outward motion most prominent in leads KV_3 and KV_4; however, it may be seen over the entire precordium. It will be noted that this is not always synchronous with the second heart sound, but corresponds more closely to the KL upstroke of the ballistocardiogram. During this upstroke* there are sometimes a few vibrations which probably represent some of the vibrations of the second heart sound.

Isometric Relaxation or Isometric Diastole

Simultaneous with the incisura of the carotid pulse there is noted a fall or an inward motion occurring prominently in KV_3 and KV_4. This is immediately followed by a general outward motion, noted in all positions, which begins before the "V" peak on the jugular tracing. If one assumes that the "V" peak represents the opening of the auriculoventricular valves, the outward motion is, therefore, not related to ventricular filling. This outward motion also corresponds to the MN upstroke on the ballistocardiograph, and, at approximately the peak of the N wave, there is a change in gradient of this pattern, or a slight inward motion which varies from one subject to the other. When the inward motion does occur, it is noted most prominently on the lateral aspect of the chest.

Rapid Filling

There are no characteristic movements noted in rapid filling, but only a continuation of the preceding movement. A change in gradient is noted, occasionally. Whether this corresponds to the end of rapid filling is not known at this time.

Auricular Systole

There is a small slow outward movement noted most frequently over the base of the ventricle, just preceding the phase of protosystole. This begins at about the peak of the P wave on the electrocardiogram, or just before the QRS deflection, indicating that this is probably the result of atrial systole. It has been noted to be absent in patients with auricular fibrillation.

Interference of the Heart-Sound Vibrations

It is apparent, from a study of the records, that all motions which have been discussed are below the range of 30 vibrations per second, or below the audible frequency range of vibrations, and represent inward and outward motions of the chest wall, occurring on the spot where the endpiece is placed. During the first heart sound, motions similar to those noted in KV_2, KV_3, and KV_4, have been recorded previously in linear phonocardiograms.[9] It seems unlikely that these inward motions are the result of only the closure of the auriculoventricular valve, since the onset of the motion is not necessarily synchronous in all positions over the anterior precordial area. One would expect that the vibrations as the result of the closure of the A-V valves would reach all anterior V leads simultaneously, and produce, in general, the same type of deflection, which is not the case. Thus other factors are probably the cause for the inward movement, and not the closure of the A-V valves, per se. Similarly, the marked outward motion occurring at or just before the beginning of protodiastole precedes the second heart sound by as much as 0.04 second, and is probably not directly related to the closure of the semilunar valves. The small higher-frequency vibrations, which occur at the peak of this outward movement, are probably the result of the second heart sound.

The Interference of the Chest Wall

It is believed that the chest wall itself has very little effect on the movements recorded,

* The peak of the KL upstroke, as recorded by the direct displacement method, and discussed in a separate communication,[7] occurs close to the time of the carotid incisura.

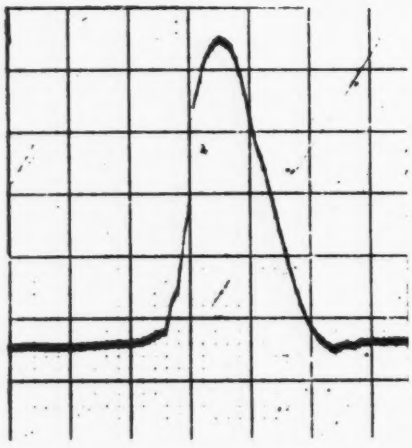

FIG. 5. A record obtained from the chest wall of a cadaver by inserting the hand into the abdomen and tapping on the chest wall from within, in the region of the apex. Note that following the marked outward motion as result of the tap, the curve comes back to the baseline with almost no overshooting, suggesting the chest wall does not actively alter the motions being recorded.

other than perhaps altering the amplitude of the record in a given individual. Studies on a cadaver, leaving the chest wall intact, inserting the hand from the abdomen and tapping the chest wall from within (both in the region of the apex and of the sternum) revealed an outward motion (fig. 5) which returned to the baseline with almost no overshooting. The response varies in amplitude with the proximity of the pickup arm to the location of the tapping. By striking the chest wall a very hard blow it was possible to set the chest into vibration at a frequency of about 50 cycles per second, which is well out of the range of motions described in this paper. Thus it appears that the chest wall has very little direct effect on the pattern of the kinetocardiogram.

It seems probable that there are many factors which are responsible for the movements of the chest wall, as recorded. These include: (1) Movements as the result of the impact of the heart against the chest wall; (2) changes in the interthoracic volume as the result of ejec-

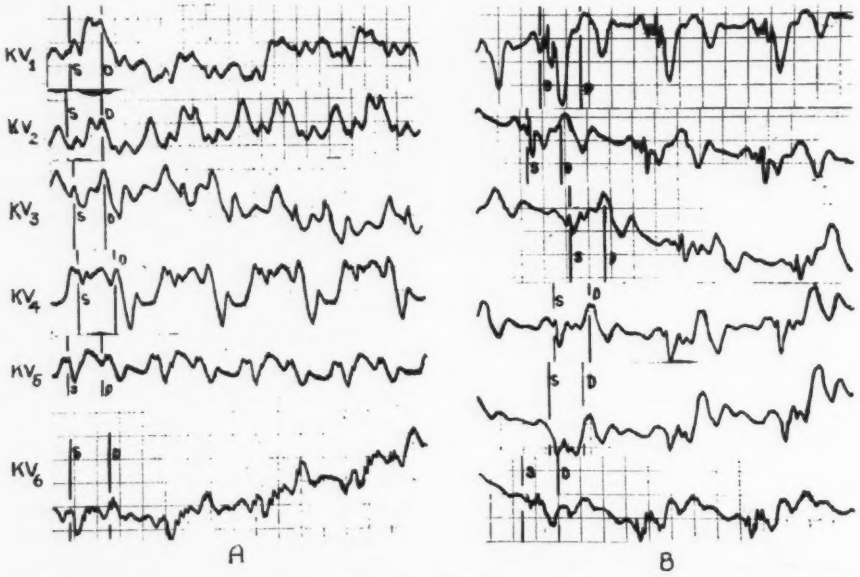

FIG. 6*A* and *B*. Illustrations of abnormal records as obtained from patients with: (*A*) severe angina pectoris; (*B*) organic mitral insufficiency. The beginning of systole is designated by the letter "S;" and the beginning of diastole is designated by the letter "D." Note the marked dissimilarity between these records and those obtained from normal individuals (fig. 2*A* and *B*, and fig. 3). In *A* it is noted that the inward motions associated with systole are much smaller in magnitude than those of diastole, and in some instances could be entirely missed if it were not for the simultaneous heart sounds and carotid pulses obtained. In figure *B* note the marked outward motion occurring in late systole, and, likewise, a marked dissimilarity between this and records obtained from normal subjects.

tion or filling; (3) phenomena of the impacts of blood in the great vessels; and (4) possible positional and shape changes of the heart. A detailed analysis of these facts will be presented in an additional communication.

Certainly, preliminary observations confirm the opinion of Johnston,[5] and Luisada[6] that totally different records are obtained in organic heart disease. Such records are even more complicated than the normal patterns, and at present the meaning of the various movements is not clear. Figures 6*A* and *B* are records obtained from a patient with severe angina pectoris, and a subject with organic mitral insufficiency. The marked difference from the normal pattern emphasizes the possible future value in the procedure in the study of heart disease.

Summary and Conclusions

1. A method for recording precordial chest movements during the cardiac cycle has been described.

2. The general pattern obtained from normal subjects is pointed out, and the relationship of these movements to the phases of the cardiac cycle and the ballistocardiogram are noted.

3. Different normal young males usually displayed similarity in records taken at corresponding points, but there are striking differences in the same individual in records taken from varying points.

4. The term "kinetocardiogram" (KCG) is introduced to designate circulatory movements as recorded from the chest wall.

Sumario Español

Un método sencillo para registrar los movimientos precordiales de frecuencia baja se presenta y se le ha denominado Kinetocardiograma para indicar movimientos resultantes del movimiento cardíaco. Los patrones normales precordiales se describen al igual que las relaciones de tiempo al ciclo cardíaco y al balistocardiograma.

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A New Index for Quantitative Ballistocardiography: The Velocity of Body Displacement

By VINCENZO MASINI, M.D., AND PAOLO ROSSI, M.D.

Calculation of the velocity of body displacement and of the momentum of the body from 100 normal ballistic tracings shows that the values of the velocity of body displacement present a small scatter (mean value 68.3 ± 13.9 mm. per second) and are independent of body weight and surface area. For uniformity of values and simplicity of calculation, which can be effected also on many abnormal tracings, it is suggested that the velocity of body displacement be used as an index of quantitative ballistocardiography.

AT PRESENT the examination of ballistic tracings includes a qualitative and a quantitative analysis. The qualitative examination is concerned with the shape of the tracings, independent of the amplitude of the various deflections, and does not require that the tracings be recorded with special calibration. Quantitative analysis, on the other hand, can be applied only to tracings recorded with ballistocardiographs that employ a swinging bed and that may be precisely calibrated.

Up to now the indexes used for the quantitative analysis of the ballistocardiogram have been: (a) the calculation of the stroke volume (SV), and (b) the calculation of the maximal cardiac force (MCF), according to Starr.[1]

Several formulas have been applied to the calculation of stroke volume, among which the one most used and most practical is the formula of Tanner[2]:

$$SV = 100\sqrt{2I + J\sqrt{C}}$$

where I and J are the areas under the I and J waves of the ballistocardiogram; C is the duration of the cardiac cycle in seconds. The values of the stroke volume obtained with this formula differ somewhat from the real values obtained with the gas analysis method which makes use of the principle of Fick.[3, 4] Moreover, it must be admitted that the calculation of the stroke volume from the ballistocardiogram is open to criticism from both a theoretic and practical point of view. (a) It has not been convincingly demonstrated that the areas under I and J are related to the amount of blood ejected from the ventricle. (b) The formula for the calculation of stroke volume should include the value of the cross-sectional area of the aorta, which is difficult to assess and can be estimated only approximately from the tables of Bazett: for this reason the formula of Tanner does not include this value but only a fixed coefficient. (c) Accurate location of the base line, and, therefore, the calculation of the areas under the I and J waves, is often difficult, especially in tracings with very large diastolic waves or marked tachycardia. (d) Finally, the calculation of the stroke volume is possible only on ballistocardiograms of normal configuration.

Recently Starr[1] has devised a new index of quantitative ballistocardiography, namely, maximal cardiac force (MCF). Experimental observation shows that the ballistocardiographic tracing represents the third derivative of the curve of the acceleration of the blood in the large vessels; therefore the amplitude of the systolic waves of the ballistocardiogram is proportional, not to the amount of blood, but to the acceleration imparted to the blood during ventricular systole. The maximal cardiac force may be calculated in per cent of a hypothetic normal value; since, however, the values of the maximal cardiac force are extremely variable, this normal value is established by a critical coefficient which, according to Starr's statistical calculations, in normal individuals ranges from 0 to 2.

There is no doubt that the calculation of the

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maximal cardiac force introduces an element of considerable interest in quantitative ballistocardiography, because it represents an index of the heart dynamics which cannot be evaluated by other methods. Furthermore, the value can be calculated on both normal and abnormal tracings, independent of the location of the base line.

In our experience,[5] however, we have noticed that the values of the maximal cardiac force in normal subjects may differ widely and also that the critical coefficient is not a reliable index, because in our cases it was found to be more than 2 in 20 per cent of normal individuals.

For these reasons we have tried to devise a new index of quantitative ballistocardiography which should fulfill the following requirements: (a) it must be easy to calculate; (b) it must be applicable also to abnormal tracings; (c) it must be a simple and direct expression of the complex hemodynamic forces which develop and act during the systolic phase of the ballistocardiogram.

Theoretic Considerations

Although the genesis of the ballistic waves has not yet been completely clarified, there is no doubt that the movements of the body, those at least which occur during systole, are due directly or indirectly (through the movement of the blood in the vessels) to the action of a force generated from a central source of energy, namely the heart.

Can the ballistocardiogram give a quantitative definition of this force? The unit of measure of a force is the dyne which corresponds to the force of 1.0 Gm. acting for 1.0 second. Obviously the ballistocardiogram cannot define in this manner the force of the heart.

An indirect means for the evaluation of a force is represented by the estimate of the work it performs. It is known that the work of the heart is expressed by the formula

$$W = P \cdot SV + \frac{SV \cdot V^2}{2}$$

where P is the mean arterial pressure; SV is the stroke volume; V is the velocity of the blood at the level of the aortic orifice.

In fact the work of the heart is represented by a static component ($P \cdot SV$) which expresses the energy expended in developing a pressure equal to the arterial pressure upon the blood ejected at each systole, and a dynamic component $\frac{SV \cdot V^2}{2}$ which expresses the energy expended in imposing a given velocity (V) on the blood mass. From the ballistocardiogram we can estimate the value of the static component but not that of the dynamic component, because we have no means of calculating the velocity of the blood. Cardiac work expressed by the value of the static component is open to criticism on the basis of the same considerations we have made regarding the calculation of the stroke volume from the ballistocardiogram, and also because the dynamic work is a negligible element under basal condition and in normal hearts, whereas it increases considerably after effort and in many forms of heart disease.

Another quantitative criterion for the evaluation of a force may be represented by the acceleration that this force imparts to the mass upon which it acts: by the second law of dynamics we know that "a force is proportional to the acceleration which it impresses on the body upon which it acts, and has the same direction as this acceleration." The force of the heart, during systole, produces an acceleration of the blood mass and of the body, the complex movements of which are precisely those recorded by the ballistocardiogram. Therefore the value of the acceleration impressed on the body by the force of the ventricular systole may be calculated from the ballistocardiogram by computing the second derivative of the ballistic curve, that is, the derivative of velocity in relation to time. This calculation is too complex to be of practical use.

An indirect method for the estimate of the magnitude of a force may also consist of the calculation of its impulse. Impulse of a force is defined as the product of the force and the time of its action, and is expressed by the formula

$$I = Ft$$

By the second law of dynamics

$$F = ma$$

where m is the mass of the body upon which the force acts, and a is the acceleration impressed on the body by this force. Multiplying both the members of the preceding equation by t we have

$$Ft = mat$$

Since $at = V$ (velocity), we can write

$$Ft = mV$$

mV is defined as momentum (M). It may be readily seen that momentum equals impulse, expressed by the same formula.

The impulse of the cardiac force may therefore be estimated by calculating the momentum impressed on the blood (and therefore on the body) during systole. The momentum is easily calculated on the ballistocardiogram, because mass equals body weight and velocity may be derived from the ballistocardiogram by measuring the distance traveled by the body and the time employed to cover it.

In reality the ballistocardiogram shows that the movement of the body during systole is not unidirectional, inasmuch as it is recorded as a polyphasic curve. Such polyphasism is probably due to the summation of the cardiac ejection force and the forces generated by the movement of the blood within the large vessels. These forces develop in different directions, mainly on account of the curvature of the aortic arch. At the present time we do not know which is the deflection caused directly and exclusively by the cardiac ejection force. We have, therefore, thought of calculating the momentum of the body during the movement inscribed from the peak of the I wave to the peak of the J wave. This movement was chosen for the following reasons: (a) since this is the greatest movement recorded by the ballistocardiogram during systole, it can be assumed that it corresponds to the maximal impulse of the cardiac force; (b) it was chosen for practical reasons, since this is the movement which can be determined with the greatest accuracy even if the ballistocardiogram is abnormal in form. We have indicated by Mb the momentum of the body thus calculated.

Not even Mb, however, represents a measure of the work of the heart because of the following considerations:

(a) The ballistic curve is polyphasic and in reality we are unable to establish the momentum of all the movements of the body.

(b) The calculated movement IJ undoubtedly is the resultant in the head-to-foot direction of many forces acting in different directions. On the other hand our present understanding of the genesis of the ballistic waves is too uncertain to establish whether, to what extent, and under what physiologic or pathologic conditions, changes in the direction of these forces may modify the resultant in the head-to-foot direction, independently of the total variance in the work of the heart.

(c) The momentum impressed on the body could be taken to represent the work of the heart provided the resistance to the ejection of the blood during the ventricular systole were always the same. Instead there are many conditions which greatly modify such resistance: among these are variations in the size of the aortic orifice and changes in the viscosity of the blood. For instance, in aortic stenosis the momentum impressed on the blood, and therefore on the body, can be greatly reduced owing to the obstacle to the passage of the blood through the narrow aortic orifice, whereas in reality the work of the heart is greater than normal.

Even with these reservations concerning the possibility of evaluating the work of the heart, it is nevertheless undeniable that the momentum impressed on the body is proportional to the momentum impressed on the blood during ventricular systole. And as the latter is the resultant of at least two main factors (ventricular ejection force and resistance), it is evident that the momentum and consequently the speed of body displacement (Vb) represent reliable quantitative indexes of the complex hemodynamic and ballistic condition of ventricular ejection.

We have, therefore, considered it useful to estimate the values of these measurements in normal persons and to establish whether they could represent a practical index of quantitative ballistocardiography.

Technic

From the ballistocardiogram of 100 healthy subjects we have calculated the momentum of the body (*Mb*) and the velocity of body displacement (*Vb*). Our cases included 52 males and 48 females ranging in age from 15 to 40 years (mean age 31 years).

The ballistocardiograms (all normal in form) were recorded at basal rest with a ballistocardiograph of our construction, which consists of a high-frequency swinging bed,[6] exactly calibrated so that release of a 280 Gm. weight displaces the base line 1 cm. The momentum (*Mb*) was estimated according to the formula

$$Mb = mVb$$

where m is the body weight in kilograms. Velocity of body displacement (*Vb*) was calculated according to the formula*

$$Vb = \frac{D}{t}$$

where D represents the distance in meters from the peak of I to the peak of J, and t is the time in seconds between the same points (fig. 1).

Thus computed, the velocity (*Vb*) is expressed in meters per second and the momentum (*Mb*) in kilogram- meters per second. For practical convenience the values of *Vb* have been reduced to millimeters per second.

Results and Comment

Maximal, mean and minimal values of the momentum of the body (*Mb*) and of velocity of body displacement (*Vb*) obtained in men, in women and in both sexes together, the values of the standard deviation (σ) and those of the standard deviation from the mean (σm) are given in tables 1 and 2.

Tables 3 and 4 show the frequency in per cent of the values of *Mb* and *Vb* in men, women and in both sexes together.

Figures 2 and 3 show the values of the speed of body displacement (*Vb*) in relation

* It may be noted that this formula corresponds to the one proposed by Nickerson[4] (IJ amplitude divided by I–J interval) for the calculation of stroke volume from ballistocardiograms recorded with a low frequency ballistocardiograph. However, the reliability of Nickerson's formula has been questioned by Brandt and associates,[7] especially during the action of drugs or diseases.

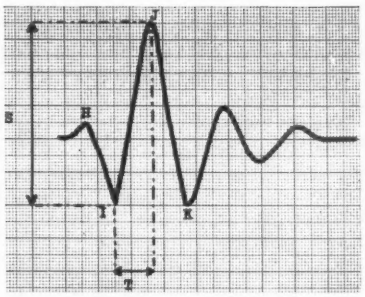

Fig. 1. Schematic representation of the measurement of distance (*S*) and time (*T*) for the calculation of the speed of body displacement (*Vb*).

Table 1.—*Maximal, Mean and Minimal Values, Standard Deviation and Standard Deviation from the Mean of the Momentum of the Body (Mb)*

$\frac{Mb}{Kg. \times M./sec.}$	Max	Mean	Min	σ	$\sigma(m)$
Men	8.80	5.12	2.69	1.33	0.18
Women	6.37	3.07	1.87	0.87	0.12
Both sexes	8.80	4.30	1.87	1.40	0.14

Table 2.—*Maximal, Mean and Minimal Values, Standard Deviation and Standard Deviation from the Mean of the Speed of Body Displacement (Vb)*

$\frac{Vb}{mm./sec.}$	Max	Mean	Min	σ	$\sigma(m)$
Men	115	76	43	17.5	2.4
Women	100	59	36	11.4	1.6
Both sexes	115	68.3	30	13.9	1.3

Table 3.—*Frequency in Per Cent of the Values of the Momentum of the Body (Mb)*

$\frac{Mb}{Kg. \times M./sec.}$	Men %	Women %	Both sexes %
1–2	1.9	2	2
2.1–3	1.9	31.3	16
3.1–4	9.6	41.8	25
4.1–5	40.5	20.9	31
5.1–6	25	2	14
6.1–7	9.6	2	6
7.1–8	9.6	—	5
8.1–9	1.9	—	1

to body weight and body surface area estimated according to the tables of Dubois.

TABLE 4.—*Frequency in Per Cent of the Values of the Speed of Body Displacement (Vb)*

Vb mm./sec.	Men %	Women %	Both sexes %
30–39	—	6.1	3
40–49	3.8	14.5	9
50–59	19.3	39.5	29
60–69	17.3	21.3	19
70–79	21.3	12.5	17
80–89	17.3	6.1	12
90–99	17.3	—	9
100–110	3.8	—	2

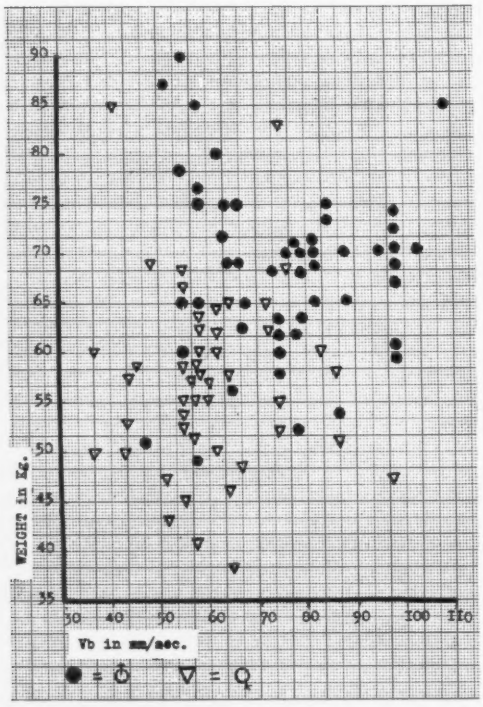

FIG. 2. The relation between the values of the speed of body displacement (*Vb*) and those of body weight.

From the foregoing findings we may conclude:

1. The mean value of *Mb* is 4.3, and the standard deviation about the mean is 1.4 kilogram- meters per second, with maximal value of 8.8 and minimal of 1.8. The figures are decidedly greater in men than in women, the mean value for women being 3.07 kilogram-meters per second, and 5.12 for men.

The values of *Vb* range from 115 to 30 mm. per second, mean value being 68.3 with a standard deviation about the mean of 13.99 mm. per second. Also, *Vb* is greater in men (mean 76 mm. per second) than in women (mean 59 mm. per second).

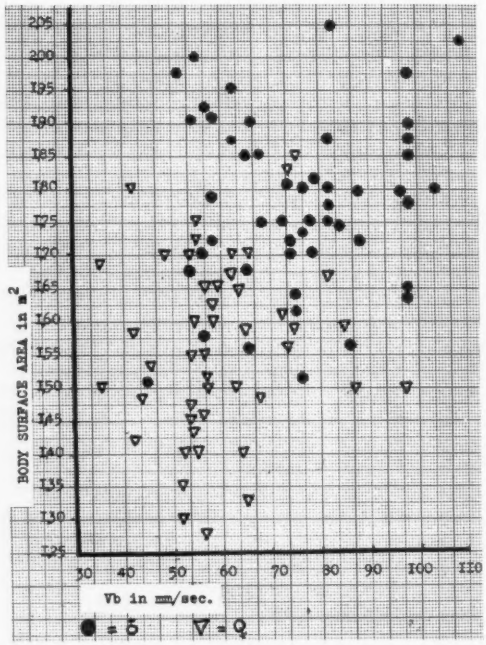

FIG. 3. The relation between the values of the speed of body displacement (*Vb*) and those of body surface area.

2. There is a direct relationship between the values of the momentum and those of body weight, inasmuch as the former is expressed by the formula

$$Mb = mVb$$

The values of *Vb*, instead, are irregularly distributed in the various groups of body weight and surface area (figs. 2 and 3). For this reason the figures of *Vb* must be considered as independent of the values of these two elements. From this it may be inferred that

the variance of *Mb* is dependent principally on the body weight and only in a small part on the value of *Mb*. In reality, therefore, *Mb* must have a greater variance than is shown in our study, inasmuch as our cases include subjects of about the same age and with little difference in body weight.

3. It seems, therefore, that *Vb* should be preferred as an index of quantitative ballistocardiography because the findings show little variance and are not related to body weight. It should also be noted that *Vb* can be estimated not only on normal tracings but also on many abnormal tracings, provided the interval I-J is still recognizable.

Conclusions

From theoretic considerations we may conclude that the momentum of the body (*Mb*) and the velocity of body displacement (*Vb*) are of interest from the point of view of pathologic physiology because they represent a quantitative evaluation of the ballistic forces generated by the complex hemodynamics of the ejection phase of the ventricular systole.

The findings show that the values of *Vb* present a small scatter in normal subjects and that, unlike those of *Mb*, they are independent of body weight and surface area. For the uniformity of the values and the simplicity of the calculation, which may be made also on many abnormal tracings, we suggest that *Vb* be used as an index of quantitative ballistocardiography.

Summary

From the ballistocardiographic tracings of 100 healthy subjects we have calculated with a personally devised method (a) the momentum of the body (*Mb*), and (b) the velocity of body displacement (*Vb*) during ventricular systole.

The mean value of the momentum of the body was 4.3 with a standard deviation about the mean of 1.4 kilogram- meters per second, and that of the velocity of body displacement was 68.3 and 13.9 mm. per second. The figures for men are higher than those for women.

We suggest that the velocity of body displacement (*Vb*) be used as an index of quantitative ballistocardiography for the following reasons: (a) the values are uniform and are independent of body weight and surface area; (b) the calculation is simple and can be made also on many abnormal tracings; (c) it is a quantitative expression of the complex hemodynamics of the ejection phase of the ventricular systole.

Acknowledgments

The authors wish to express their appreciation and gratitude to Dr. Isaac Starr for his consideration of the manuscript and his helpful suggestions.

Sumario Español

La calculación de la velocidad de desplazamiento del cuerpo y del momento del cuerpo en 100 trazados balísticos demuestra que los valores de la velocidad del desplazamiento del cuerpo presentan un pequeño esparcido (valores promedio 68.3 ± 13.9 mm. por segundo) y son independientes al peso del cuerpo o al area de superficie. Para la uniformidad de los valores y la simplicidad de calculación que se puede efectuar también en muchos trazados anormales, se sugiere que la velocidad de desplazamiento del cuerpo se use como un índice quantitativo de balistocardiografía.

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Long-Range Observations of Sodium Exchange in Patients with Congestive Heart Failure

By JOHN A. LUSK, III, M.D., AND S. DONALD PALMER, M.D.

Long-term studies of sodium balance were made in three patients with congestive failure. The data indicate exchange of water and sodium between the intracellular and extracellular spaces. They suggest that a portion of the intracellular cation exists in a form which is not osmotically active. The term "quantometer" is applied to the previously described intracranial volume-regulating mechanism. An hypothesis is offered in which it is assumed that exhaustion of this quantometer may contribute to the retention of sodium as heart failure becomes manifest.

THE starting point of the reports from this laboratory[1-7] was the desire to investigate the concept of a central homeostatic mechanism concerned with sodium retention as a means of protecting the body against various types of circulatory failure. With the exception of two reports[6, 7] these studies have been limited to normal subjects and are not, therefore, directly applicable to patients with cardiac failure, or to such problems as the importance of the orthopneic position in relation to edema formation. The observations reported thus far seem to indicate that a central homeostatic mechanism concerned with sodium exchange does exist, and that this mechanism is brought into play not by a decline in cardiac output or alteration of renal hemodynamics, but rather by alterations in the renal tubular activity initiated by a change in the distribution and volume of body fluids. Since the results of the data recently collected from studies on patients with congestive failure[6, 7] indicate that this homeostatic mechanism is greatly impaired or is inoperative in congestive failure, it seemed advisable to observe patients with congestive failure for longer periods of time. It was hoped that a clearer concept of the role of this homeostatic mechanism in the formation of edema in cardiac failure would emerge. The present report is concerned with the long-range observations of the sodium exchange in three patients with chronic congestive heart failure.

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This work was aided by a grant from the Life Insurance Medical Research Fund.

This work was done during Dr. Lusk's tenure of a U. S. Public Health Service Postdoctorate fellowship, and during Dr. Palmer's tenure of a Life Insurance Medical Research Fellowship.

METHODS

The observations reported here were made on three patients with congestive heart failure due to rheumatic mitral stenosis (A.S.), senile heart disease (J.T.), and cor pulmonale with senile heart disease (J.M.). All were able to deliver urine with a maximum specific gravity of 1.025 or higher. The clinical course of each patient was followed by frequent determinations of venous pressure, circulation time, vital capacity, and blood pressure. Dietary sodium was calculated from weighed diets.[8*] Water intake (distilled water), urine volumes and body weight were recorded daily.

Serum and urine analyses for sodium were made with a Beckman DU model photometer, utilizing an oxyacetylene type flame.

Calculations were based on the assumption that daily weight changes represented changes in extracellular water, that is, edema fluid.

Calculations

1. Extracellular sodium concentrations [(Na_{ECF})] were considered to be 0.95 × serum concentration.
2. Changes in extracellular sodium (ΔNa_{ECF}) equalled change in body weight (Δwt.) × extracellular sodium concentration [(Na_{ECF})].
3. Total sodium balance (ΔNa) = intake (Na_I) − output (Na_O) of sodium.
4. Changes in "nonextracellular" sodium (pre-

* The Lonalac used in the preparation of these diets was kindly furnished by Mead, Johnson and Company, Evansville, Ind.

imably intracellular sodium) content (ΔNa_{ICF}) = $\Delta Na - \Delta Na_{ECF}$.

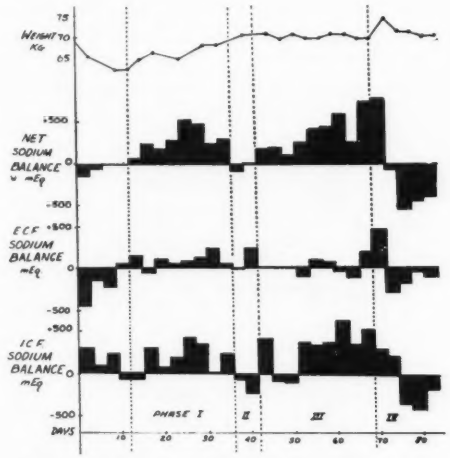

FIG. 1. Patient J. T. On admission he was given a diet containing 2.5 mEq. of sodium per day. During the following 12 days his weight fell from 69.0 Kg. to 62.2 Kg., and the sodium balance was negative. Calculations revealed an initial loss of sodium from the extracellular space and an apparent increase in intracellular sodium. During the eleventh and twelfth days urine volumes declined, and serum sodium concentration fell to 126 mEq. per L. (It had previously been within normal limits.)

From the thirteenth to the seventy-third hospital day the patient received a 250 mEq. sodium diet daily. During the period from the thirteenth to the thirty-sixth day there was a slight weight gain, a positive sodium balance, with an increase in both extra- and intracellular sodium.

The next six days revealed a state of relative equilibrium in so far as sodium exchange was concerned.

During the period from the forty-third to sixty-ninth day, J. T.'s subjective and objective condition showed little change. Weight changed only slightly. On the other hand, there was a strikingly positive sodium balance, practically all being taken into the intracellular space.

The next three days were characterized by a deterioration of the patient's condition, an increment in body weight, and an increase in extracellular sodium.

After the institution of a diet containing 2.5 mEq. of sodium per day on the seventy-ninth day, the changes noted during the first 12 days were observed.

RESULTS

I. *Sodium-Rich Diets. (Figs. 1 and 2)*

Patient J. T. (Fig. 1). Following an oliguric episode due to sodium depletion, patient J. T. (fig. 1, days 15 through 72) was placed on a diet containing an average of 250 mEq. of sodium per day, and digitalis therapy was discontinued. In so far as sodium exchange was concerned, his response to this high sodium intake may be divided roughly into four phases.

Phase I: *Recovery from sodium depletion (days 12 to 36, fig. 1).* During this period there was a slight gain in weight, with a positive sodium balance. On analysis it was found that this sodium was retained in both the extracellular and the calculated intracellular compartments, with slightly more sodium being held in the latter.

Phase II: *Interval of relative sodium equilibrium (days 37 to 42).* This period was characterized by its brevity and by a relative balance between intake and output of sodium. In general, both extracellular and calculated intracellular compartments showed equal uptake of sodium.

Phase III: *Positive intracellular sodium balance (days 43 to 69).* With a slight gain in weight, there was a strongly positive sodium balance, extracellular sodium showing comparative equilibrium and the calculated intracellular compartment receiving almost all of the retained sodium. Neither subjectively nor objectively (venous pressure, vital capacity, circulation time) were there noticeable changes in the patient's condition.

Phase IV: *Development of clinical congestive failure (days 70 to 73).* In contrast to the preceding phase, sodium was retained in both extra- and intracellular compartments. The patient rapidly gained weight, developed orthopnea, pedal edema, increased venous pressure and circulation time, and a diminished vital capacity. Daily urine volume which previously had been roughly equated to water intake became much less than fluid intake.

Patient J. M. (Fig. 2). The institution of a diet rich in sodium in this patient was, like the above patient, preceded by an episode of sodium depletion, which had been accomplished by a severe restriction of dietary sodium (3 to 5 mEq. per day). Digitalis was withdrawn in this instance and daily sodium intake was, on the average 220 mEq. Clinically, J. M.'s

cardiac failure was of a more severe degree than that of J. T.

The first two phases described for J. T. were either nonexistent or were too transitory to be apparent with daily collection periods. The phase of positive intracellular sodium balance was the only one observed with this patient.

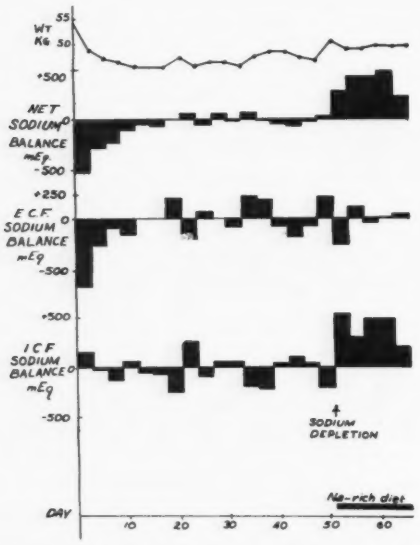

FIG. 2. This patient was ambulatory on admission, and exhibited only a minimal degree of decompensation. After placing him on a 3 to 5 mEq. sodium diet there was a loss of weight and of sodium. The sodium was lost from the extracellular space, while the intracellular compartment showed an increased sodium content.

On the forty-eighth day the patient began to display clinical evidence of sodium depletion. There was an increase in weight without a concomitant increase in body sodium. Serum sodium concentration fell to 132 mEq. per liter.

After being placed on a diet containing 220 mEq. of sodium (fifty-second day) there was a slight fall in weight and a strongly positive sodium balance, with practically all being retained intracellularly.

This balance study was terminated before clinical manifestations of congestive failure were observed.

II. *Sodium Restriction and Recovery from Congestive Failure.* (*Figs. 1, 2 and 3*)

Patient A. S. (*Fig. 3*). On admission, this patient exhibited the usual signs of severe congestive failure, such as pulmonary edema pedal edema, and marked orthopnea. Hi therapy consisted of digitalis, bed rest, and restricted sodium intake. Initially, there was

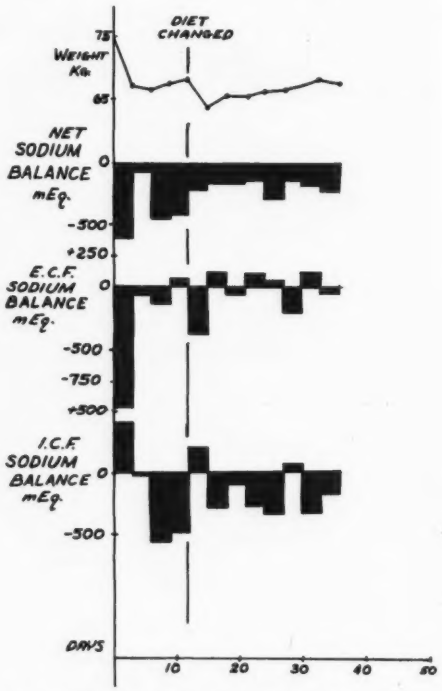

FIG. 3. On admission this patient exhibited severe manifestations of congestive failure. He was initially placed on a diet containing 13 mEq. of sodium. There was a sharp weight loss and a negative sodium balance. The extracellular space lost sodium, and the calculated intracellular compartment showed an increased content of sodium. After this initial three-day period sodium was lost from the intracellular space.

On the twenty-third day the patient's diet was changed to one containing 6.5 mEq. of sodium. The changes described above were repeated, though they were of lesser magnitude.

Throughout the remainder of the study sodium continued to be lost from the intracellular compartment in greater quantities than the extracellular space.

sharp drop in weight, and a loss of sodium, with urine containing sodium at a lesser concentration than that of the extracellular fluid. Calculations revealed that concomitant with this there was an increase in intracellular sodium content. After this initially positive

intracellular sodium balance, there occurred an outpouring of sodium from this compartment. On the twelfth day a change in dietary sodium content from 13 mEq. per day to one containing 6.5 mEq. per day was followed by a decline in weight, a negative extracellular sodium balance, and a positive intracellular balance, though to a lesser extent than that following admission. The remainder of the study showed loss of sodium from both compartments. Objective and subjective clinical improvement was manifest over the entire period of study.

Patient J. T. (*Fig. 1*). This patient was ambulatory on admission and had only moderate pedal edema. There was no detectable pulmonary congestion, and measurements of the cardiac status indicated a moderate state of decompensation. Therapy again consisted of sodium restriction, bed rest, and digitalis. Following the institution of sodium restriction, the observed and calculated balances of sodium were parallel to those of A. S. (fig. 3).

Following the development of congestive failure described previously, sodium restriction was again instituted. The results were similar in all respects to those described previously.

Patient J. M. (*Fig. 2*). The degree of congestive failure presented by this patient was minimal. After institution of a diet with low-sodium content there was a negative balance of this cation, with practically all being withdrawn from the extracellular space.

Comment

As stated previously, it was initially assumed that changes in weight represented changes in extracellular fluid or edema, and all calculations were made on this basis. It can be seen (figs. 1, 2 and 3) that in patients recovering from congestive failure, water is excreted in such proportions to sodium that the urine contains a lesser concentration of sodium than the serum. This can be interpreted in one of two ways: either that sodium is temporarily taken into the cells, or that water was withdrawn from the cells to contribute to the production of a urine with a lower sodium concentration than extracellular fluid. In view of the observation that prior to the development of overt congestive failure, sodium is apparently stored intracellularly without an increase in body water, and that failure develops after what may be presumed to be a "cellular saturation" with sodium, it hardly seems possible for as much of this cation to move into the cells on recovery from failure as is shown by our calculations.

Squires and coworkers[9, 10] in their study found that patients recovering from edema by diuresis lost water from the intracellular space, and that urine contained less sodium than serum. Therefore, the initial assumption that water loss represents only extracellular fluid is not entirely correct, and the data presented will be discussed with this in mind.

It is realized that the patients studied here were probably undergoing changes in nitrogen balance and hence the weight change did not represent solely changes in body water. The previous dietary history obtained from these patients and the results of other studies[9, 10] indicated that a positive nitrogen balance was likely during the present studies. Therefore, the basis on which the data were calculated would show greater than actual increase in extracellular sodium. During periods of rapid weight changes it would seem unlikely that protein changes would be significant.

Discussion

The data presented show that during the diuresis which accompanies recovery from congestive heart failure, there was initially a loss of both extra- and intracellular water and extracellular sodium. As clinically manifest heart failure developed, there was apparently a large increment in intracellular sodium before extracellular sodium and total body water began to increase. After the retention of water began, clinical failure developed rapidly.

If the sodium does in fact enter the cells in large quantities as congestive heart failure develops, there would seem to be four possibilities in regard to osmolar changes:

(a) That there is a corresponding rise in intracellular osmotic pressure. Since extracellular sodium concentration (and therefore presumably extracellular osmotic pressure)

does not rise, it seems unlikely that intracellular osmolarity would increase.

(b) That as sodium enters, water also enters in corresponding quantities, so that no change in intracellular osmolarity occurs. The simultaneous lack of weight gain and of rise of extracellular sodium concentration mitigates strongly against this assumption.

(c) That excess intracellular sodium is balanced by equimolar losses of some other cation. The available evidence does not seem to support this conclusion[9, 10] in so far as potassium is concerned. It would appear that the amount of magnesium present in cells is not sufficient to balance this sodium gain, even if most of this ion were lost from the cells.

(d) That the increased intracellular sodium does not appreciably alter cellular osmolarity. Therefore, it would seem likely that the sodium, or some other ion, becomes bound into an unionized or inactive form, and minimal or no changes in osmotically active cellular base occur. It is not inconveivable that this inactivation of cellular base is due to changes in the size and degree of dissociation of various phosphate and proteinate molecules which take place during the processes of cellular metabolism. Other investigators[11-15] have found that similar apparently paradoxic transfers of sodium occur with diuresis during recovery from congestive failure. Their conclusions are similar to those presented.

As stated previously, the intitial purpose of these reports[1-7] was to investigate the nature of a central homeostatic mechanism concerned with the regulation of sodium exchange as a means of protecting the organism against circulatory failure. Studies from this laboratory[6, 7] suggest that this mechanism does not function in patients with congestive failure. Why does it not operate in heart failure, and how does this affect sodium exchange? Does the failure of this volume-regulating center influence the formation of edema in heart failure? At the present time these questions can be answered only in a speculative way, and only by the use of inference and analogy.

The adjustments in effective osmotic pressure which are made by the body are apparently affected mainly through the regulation of water excretion via the posterior pituitary antidiuretic hormone. This mechanism has been nicely presented by Verney[16] and O'Connor,[17] and Peters[18] has referred to this as the "osmometer."

The control of the volume of body fluids cannot be so easily defined as that of osmotic regulation. Although osmolarity is the same throughout the cardiovascular system, the distribution of body fluids is profoundly influenced by such factors as gravity and posture. The evidence seems to support the concept of a volume-regulating mechanism (hereinafter referred to as the "quantometer"), responding to volume changes and mediating its response through sodium excretion.[1, 6]

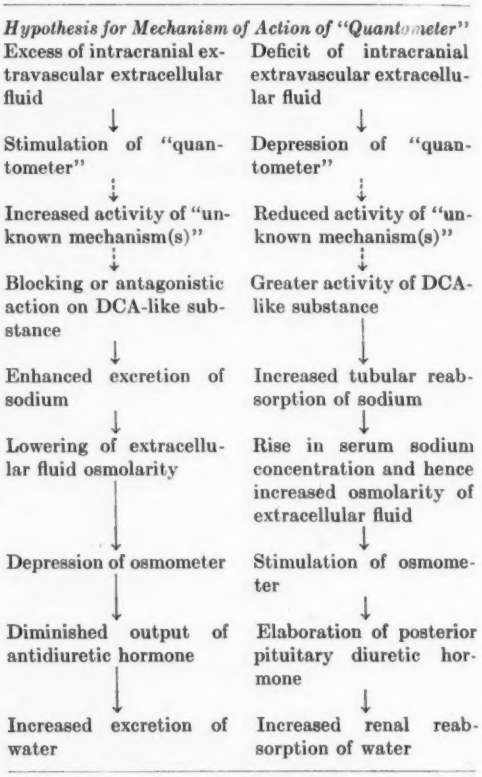

FIG. 4. See text.

One hypothesis which explains a possible mechanism of action of this "quantometer" is presented in figure 4. This concept is to be

considered highly speculative, and final acceptance must await more definitive evidence than is presently available.

It has been reported by Gaudino and Levitt[14] that an adrenal cortical hormone [a desoxycorticosterone (DCA)-like compound] has a primary influence on the distribution of sodium between extracellular and intracellular compartments. Their report states that this desoxycorticosterone-like substance produces a decrease in intracellular fluid space, and an increase in the extracellular fluid space. Desoxycorticosterone caused an increase in total body sodium with an elevated intracellular concentration of this cation. Adrenalectomy reversed these effects. That the renal tubular cells are more sensitive than other body cells to this compound is a conclusion which naturally follows, since they report a rise in serum sodium concentration under its influence.

As shown in figure 4, the "quantometer," through unknown mechanisms, exerts an influence on the activity of circulating desoxycorticosterone (or desoxycorticosterone-like compounds). It has been shown that patients with therapeutically controlled Addison's disease respond to posture with changes in sodium excretion much the same as do normals.[19] Therefore, it would seem unlikely that the "quantometer" would influence the secretion of a desoxycorticosterone-like substance. Consequently, it is assumed that stimulation of the "quantometer" leads to a depression of the activity of some desoxycorticosterone-like substance. This antagonistic action affects the renal tubular cells (and to a lesser extent other body cells), so that less sodium is reabsorbed from the glomerular filtrate.

In figure 5 an outline of a possible mechanism leading up to clinically manifest heart failure is shown.

It is assumed that in congestive heart failure there occurs with activity a redistribution of blood into the central vessels and great veins of the thorax.[20] Since there is an accumulation of greater than normal quantities of blood away from the periphery, then a deficit must exist in the systemic circulation. The occurrence of this peripheral volume deficit is assumed to depress the "quantometer," thereby effecting a retention of sodium, and subsequently (via the osmometer) of water also. Thus the ambulant and active patient with congestive failure retains during the day quantities of sodium and water in excess of a normal subject. The elimination of this excess body fluid and sodium at night, when gravity and recumbency cause a redistribution of the volume of fluids toward the head, stimulates

Hypothesis for Role of "Quantometer" in Congestive Heart Failure

1. Diminished cardiac reserve
↓
2. Central accumulation of blood
↓
3. Deficit of volume of extracellular fluid in the periphery, particularly in the cranial cavity
↓
4. Depression of "quantometer"
↓
5. Greater than normal retention of sodium; and through osmometer, increase in body water
↓
6. Recumbency at night → Redistribution of volume of body fluids → Stimulation of "quantometer" → Increased excretion of sodium and water → NOCTURIA
↓
7. Failure of effectiveness of "quantometer"
↓
8. Progressively greater retention of sodium and water → Increased pooling of blood in central vessels → Pulmonary congestion
↓
9. Orthopnea → Almost continual depression of residual activity of the "quantometer" (enhanced by gravity and posture)
↓
10. Intensification of disturbed volume and distribution of body fluids, and development of imbalance of intracellular cation content
↓
11. Clinically manifest congestive failure

FIG. 5. See text.

the "quantometer" and over a long period of time might serve to exhaust or fatigue it so that the uncontrolled retention of sodium occurs. It is conceivable that the "quantometer" is depressed during the upright posture and fails to recover its complete effectiveness when minimal activity is required. This effect would be cumulative. This offers a possible explanation of the positive sodium balance

seen in patients J. T. and J. M. (figs. 1 and 2) on sodium-rich diets. If this occurs (and it is yet to be proved) then an hypothesis exists to explain the nocturia of failure which occurs as one of the earliest symptoms of a weakening myocardium.

It has been found recently[6, 7] that patients with advanced congestive failure, requiring frequent injections of diuretics for maintenance, do not respond to compression of the neck with an increased sodium output; neither do these individuals exhibit a negative sodium balance, as do normal subjects,[1, 2] when placed in a recumbent position. If, as is shown in figure 5, the "quantometer" of such patients has failed or is not functioning adequately, then an hypothesis exists which explains their lack of response to compression of the neck and to posture.

Summary and Conclusions

The results of sodium balance studies on three patients with cardiac failure have been presented. These patients apparently exhibited striking transfers of sodium and water between the intra- and extracellular spaces of the body. In one patient given large amounts of sodium, it was shown that expansion of the extracellular fluid space did not occur until after "saturation" of the intracellular fluid space with sodium had occurred.

The results of this study have been discussed. A speculative hypothesis concerned with a mechanism of sodium retention leading up to clinically manifest heart failure has been presented.

Sumario Español

Estudios por largo tiempo de balance del sodio fueron hechos en tres pacientes con decompensación cardíaca. Los datos indican intercambio del agua y el sodio entre los espacios intracelulares y extracelulares. Se sugiere que una porción del catión intracelular existe en una forma que es osmoticamente inactiva. El termino "cuantómetro" se aplica el previamente descrito mecanismo de regulación volumétrica intracranial. Se sugiere una hipótesis en la cual se asume que el agotamiento de este cuantómetro puede contribuir a la retención del sodio a medida que la decompensación cardíaca se manifiesta.

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CLINICAL PROGRESS

Editor: HERRMAN L. BLUMGART, M.D.

Associate Editor: A. STONE FREEDBERG, M.D.

Diagnosis and Prevention of Bacterial Endocarditis

By ARTHUR L. BLOOMFIELD, M.D.

ALTHOUGH scattered early reports are recorded of probable subacute bacterial endocarditis, clear recognition of this disease as different from nonbacterial (rheumatic) endocarditis on the one hand and acute septic (ulcerative) endocarditis on the other was not accomplished until the first decade of the century; doctors in general were not correctly diagnosing subacute bacterial endocarditis until the twenties. Our present discussion concerns diagnosis and prevention; those who wish to read the interesting story of the development of the subject are referred to the articles of Blumer,[1] of Thayer[2] and of Longcope.[3]

DIAGNOSIS OF SUBACUTE BACTERIAL ENDOCARDITIS

Clinical Diagnosis

Although blood culture (see below) is paramount in the diagnosis of bacterial endocarditis, the clinical features include a constellation of findings so characteristic that as a rule the condition can be recognized by history and physical examination alone.

1. The Cardiac Lesion. Since the essence of the disease is the implantation of bacteria on a previously damaged endocardium or at the site of a congenital defect, signs of a cardiac lesion are rarely lacking. In some 90 per cent of the cases an area of rheumatic damage, usually of the mitral valve, less often of the aortic, is the site of infection. The tricuspid and pulmonic valves are much less frequently involved. Congenital lesions are at fault in approximately 5 per cent of the cases; bicuspid aortic valves, patent ductus arteriosus, interventricular septal defects, coarctation of the aorta and pulmonic stenosis are of greatest importance.[4] Curiously enough, auricular septal defects are rarely implicated. Rheumatic as well as congenital lesions may, of course, exist in the same patient. Aortic valves injured by syphilis alone are rarely, if ever, the site of bacterial endocarditis; the validity of the few reported cases is variously judged. At any rate, syphilis is certainly not a significant predisposing cause.[5] In somewhat less than 5 per cent of the cases, bacterial implantation seems to have taken place in undamaged endocardium; at least the pathologist finds no definite evidence of an antecedent lesion.

2. Fever. While fever is the rule, no special type of temperature curve is characteristic of bacterial endocarditis. There may be low irregular elevations or high "septic" fever of intermediate grades. Chills may suggest malaria. Of especial importance from the diagnostic standpoint are the afebrile periods which occur in some cases. Such absence of fever by no means always means a healed or bacteria-free stage of the disease, as shown by the afebrile periods in patients who have had suppressive but subcurative doses of an antibiotic.

3. Petechiae are of especial importance in diagnosis and should be carefully looked for. The tiny white-centered lesions often found in the palpebral conjunctivae as well as in the skin are thought to be especially suggestive of bacterial endocarditis in contrast with the larger purpuric spots which may be found in a

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ariety of infections. Petechiae may be few nd scattered, or the body and legs may be eppered with profuse crops. In a doubtful ase petechiae are especially important; in ne patient the discovery of a single typical esion under the tongue clinched the diagnosis. There is no regular correlation between the umber of spots and the degree of bacteremia; owever, the most profuse crop we have seen ccurred in a woman with over 400 colonies of *Streptococcus viridans* per milliliter of blood. The little "splinter" hemorrhages seen at times nder the nails are of less importance than petechiae; the painful swollen finger tips (Osler's nodes) also have diagnostic significance.

Petechiae must be distinguished from punctate telangiectases. The latter are bright red, they do not fade in a day or two as petechiae do, and they can be felt as slight elevations. Scrutiny of a doubtful spot with a strong magnifying glass usually helps to identify its nature.

4. Palpable Spleen. In our experience the spleen is almost always palpable even in "early" cases of bacterial endocarditis. The enlargement is usually not great, however, except in the occasional splenomegalic type of the disease to be mentioned below. In doubtful cases splenic enlargement may be decisive in pointing to the correct diagnosis.

5. Clubbing of the finger tips develops early in many patients with bacterial endocarditis and is a very valuable addition to the constellation of diagnostic findings. This sign has not been sufficiently emphasized in many accounts of the disease.

6. Embolic phenomena occur at some time in most cases since bits of vegetation are prone to break away and plug a peripheral artery. Effects of emboli are of the greatest importance in diagnosis. The clinical findings are varied and depend, of course, on the location of the occluded vessel. Overt embolism of peripheral arteries is less common than plugging of internal vessels. In the abdominal viscera the usual signal is pain; in the lungs the evidences of infarct may be found. Cerebral emboli produce neurologic signs appropriate to the area served by the occluded vessel.

Laboratory Tests

1. Blood Culture. Isolation of the causal organism by blood culture has always been paramount in the diagnosis of bacterial endocarditis. The procedure is now doubly important since selection of the proper antibiotic depends on the bacteriologic findings. Nonhemolytic streptococci of the *S. viridans* group are by far the most common causal agents[6]; they are obtained in approximately 90 per cent of the cases. Next in importance but much less frequent are pneumococci and *Hemophilus influenzae* (Blumer). In Thayer's series the gonococcus ranked third. Almost any organism, however, may on occasion produce the usual picture of subacute bacterial endocarditis; it would serve no useful purpose to give a complete list, but a few of the less common agents may be mentioned: bacterioides, *Streptobacillus moniliformis,* chromogenic bacteria, actinomyces, spirillae, fungi, etc. Marion Jones[7] in a complete and useful review of the subject lists no less than 49 organisms of all sorts, exclusive of streptococci, obtained from cases of subacute bacterial endocarditis.

Positive blood cultures are often difficult to secure; in a suspicious case numerous attempts should be made using a variety of methods. In addition to the inoculation of the usual broth flasks, agar plates should be poured with the addition of 0.5 to 2 ml. of blood. These plates should be kept moist so that they will not dry out before slowly growing colonies appear. Anaerobic methods should be tried and deep tubes of ascites dextrose agar to which 1 or 2 ml. of blood is added furnish various grades of oxygen tension. In one of our cases a single colony of *S. viridans* obtained on the fourteenth culture confirmed the clinical diagnosis. Some of the reasons for failure to obtain positive blood cultures from patients in whom bacterial endocarditis is found at autopsy are the following: (1) There may be very few organisms in the blood stream and the samples drawn actually contain no bacteria. (2) The organisms may fail to grow or they may multiply very slowly. (3) The bacteria may be filtered out and destroyed in the internal organs, or (4) the organisms may be

"sealed" within the vegetations. This whole question, so important from the standpoint of diagnosis, is fully discussed by Mallen[8] and by Beeson.[9] The number of colonies obtained in culture may vary up to several hundred per milliliter of blood; the degree of bacteremia has, however, within wide limits no special diagnostic or prognostic significance. In cases of suspected implantation on coarctation of the aorta, blood for culture should be drawn from the foot rather than the arm.

Bacteria-free and Healed Cases. It is possible that an occasional instance of bacterial endocarditis heals spontaneously, but permanent recovery is excessively rare. The subject is thoroughly reviewed by Kelson and White.[10] As a rule, so-called bacteria-free cases, that is, those with persistently negative blood cultures, are in fact active, with the bacteria more or less walled-off in the vegetations just as they may be in some cases imperfectly "cured" by antibiotics.[11] When such patients die, bacteria are often readily grown from the vegetations or at least are clearly seen in sections. It is therefore of the greatest importance for the doctor to have confidence in his clinical diagnosis of bacterial endocarditis so that the patient will not be deprived of therapy merely because the blood culture is negative.

2. Urinary Findings. The discovery of an excess of red blood cells in the urine has long been regarded as important confirmatory evidence of bacterial endocarditis. It is now known that there are two forms of renal lesion (glomerulitis), either or both of which may be present and responsible for the urinary changes. The so-called focal embolic glomerular lesions emphasized by Löhlein in 1910 and fully described by Baehr[12] in this country in 1912 consist in the involvement of one or more loops of individual glomeruli. The process is said to be specific of *S. viridans* endocarditis, but it is not certain that the local glomerular lesions are actually caused by minute emboli. In addition, changes indistinguishable from the usual varieties of diffuse glomerular nephritis may occur. We have in our files several autopsy reports in which both types of lesion are described in the same kidneys. One may discover, therefore, in the urinary sediment anything from an abnormal number of red blood cells to the full findings of glomerular nephritis. However, the urine may show no abnormality and one must remember that this does not rule out bacterial endocarditis. Bursts of frank renal bleeding, perhaps with flank pain, may be associated with gross embolism and infarct of the kidney; erroneous diagnosis of renal calculus or pyelonephritis may be made. This aspect of the subject is reviewed by Christian.[13]

3. The Blood Count. Most patients develop progressive and sometimes extreme anemia which may be severe enough to cause confusion with "hematologic" disease (see below). The usual leukocyte count is slightly elevated but it may be as low as 2000 to 3000 or as high as 30,000 to 50,000. Pepper has made systematic studies of the blood in subacute bacterial endocarditis.[14]

Differential Diagnosis

Subacute bacterial endocarditis is especially prone to masquerade as some other disease. In the early days before most doctors were alert to the correct possibility, a diagnosis of tuberculosis, typhoid fever, malaria, septic infection, brucellosis, rheumatic fever, acute rheumatoid arthritis, or unexplained fever was likely to be made. Kelson and White[10] have made a careful analysis of diagnostic errors; they list 40 conditions which were erroneously diagnosed in their 250 cases before bacterial endocarditis was recognized. Such a miscellaneous catalogue is of little help, however; it may be more useful to enumerate certain situations which require special comment:

1. Confusion with Primary Renal Disease. Bacterial endocarditis may be overlooked and a diagnosis of uremia resulting from glomerular nephritis or pyelonephritis erroneously made in the occasional case in which the renal disorder dominates the picture. All the usual evidences of renal insufficiency may be present. Villarreal and Sokoloff have described such cases.[15] In a recent patient of our own the urinary findings suggested glomerular nephritis and blood creatinine was 6 mg. per 100 ml. There was no fever but there were heart mur-

murs and an enlarged spleen. The patient died in uremia and at autopsy typical vegetations were found on the mitral valve. The kidney showed both "focal" glomerular lesions and the picture of a diffuse glomerular nephritis.

2. Confusion with Hematologic Disease. In patients with very severe anemia the presence of subacute bacterial endocarditis may be overlooked, the heart murmur being regarded as simply of "hemic" origin. One may seek in vain for a source of blood loss or other explanation of the low blood count. Petechiae and palpable spleen may suggest purpura hemorrhagica. An occult cancer with severe anemia may be erroneously diagnosed. The moral of all this is that one must think of bacterial endocarditis in every instance of severe anemia not otherwise fully explained. The situation is still further complicated by the occasional instance of bacterial endocarditis with huge spleen, anemia and leukopenia which can easily masquerade as some form of congestive splenomegaly.

3. Emboli. When the effects of an embolus dominate the clinical picture, the presence of bacterial endocarditis may be entirely overlooked. Embolism of brain may be confused with an ordinary cerebrovascular accident. Meningitis, meningoencephalitis, subarachnoid hemorrhage and mycotic aneurysm have all been described as overshadowing the underlying bacterial endocarditis.[16] An arterial embolus in the leg may draw attention away from the bacterial infection, or a renal embolus with chills and fever may be misdiagnosed acute pyelitis. Examples could be multiplied indefinitely and no easy rule for avoiding such mistakes can be laid down.

4. Confusion because of Absence of Murmurs. The diagnosis of bacterial endocarditis may occasionally be missed because no cardiac murmur is heard. Such absence of murmur may occur in rare cases where vegetations are scant and perhaps confined to the auricular walls or to the pulmonary artery, in tricuspid lesions and with certain congenital lesions. But only a very occasional case will fail to show some signs of a cardiac lesion. Examples of absence of murmurs in patients with lesions confined to the right side of the heart are given by Barker.[17]

5. Neurosis. In some cases of bacterial endocarditis with low grade infection, little if any fever, vague aches and pains and perhaps only a soft mitral systolic murmur, an erroneous diagnosis of "neurosis" may be made.

6. Bacterial Endocarditis in the Aged. It has been pointed out that in the aged the frank features of subacute bacterial endocarditis may be so modified as to elude diagnosis.[18] In an old person who continues to fail vaguely, perhaps with a little fever, after urologic manipulations, tooth extraction, various surgical operations or a respiratory infection, the possibility of bacterial endocarditis should be considered.

Early Diagnosis

It is of vital importance to the patient that an early diagnosis of bacterial endocarditis be made. If the situation is recognized before vegetations are large and destructive, and before serious embolism has occurred, "cure" may be effected by the proper antibiotic and the patient may be as well as before the bacterial implantation took place. We have a number of such cases in our series who have now remained well for nearly 10 years without any deterioration of their cardiac status. It is common experience, however, that patients often go for many months with overt bacterial endocarditis without a correct diagnosis being made. How can this be obviated? Above all, one must maintain a high index of suspicion; the doctor must have bacterial endocarditis in the forefront of his mind with all sorts of conditions. He should think of bacterial endocarditis in anyone with congenital or rheumatic heart disease who has anemia, fever, or unexplained failure of any sort. It has been shown that streptococci commonly enter the blood stream after tooth extraction,[19] operations on the nose or throat and after urologic manipulations.[20] In one of our cases a chronic suppuration of a finger seemed to be the portal of entry. While such transient bacteremias are harmless in most people, the incidence of bacterial endocarditis in those with a cardiac lesion is alarmingly high after tooth extraction or other

oral manipulations. Abortion or even normal delivery may be the source of infection. The urinary and genital tracts are common sources of enterococcal endocarditis, a variety of infection much more difficult to extirpate than that caused by the usual *S. viridans*. It is essential, therefore, that the doctor watch every patient with a cardiac lesion who is subjected to trauma of the sort mentioned above for several weeks at least, so that bacterial implantation can be promptly detected.

In this connection a word on the early symptoms is in order. Among 33 of our recent cases in which diagnosis was confirmed at autopsy, *fever*, either alone or with weakness, malaise, aches and pains, chills or weight loss, but without localizing symptoms, was the initial complaint in 22. Shortness of breath and ankle swelling were the first symptoms in four cases, chest pain was prominent in three, hemiplegia was the first manifestation in one, as were palpitation and pain in the flank.

Erroneous Diagnosis of Bacterial Endocarditis

Fever occurring in a patient with old valvular heart disease does not always mean that bacterial endocarditis has developed. Such fever may be due to recrudescence of rheumatic fever, to pulmonary infarct, or to some entirely independent intercurrent febrile disease. If petechiae seem to be present, bacterial endocarditis is almost sure to be diagnosed; one must be certain that the tiny red spots are indeed hemorrhages into the skin and not punctate telangiectases. Blood culture is, of course, specially important. In patients with valvular disease and fever but with no other clinical or bacteriologic proof of bacterial endocarditis, the question of whether to give antibiotic therapy is a difficult one. If in doubt it seems wiser to give a course of penicillin, perhaps combined with streptomycin, rather than to fail to treat a possible implantation.

Prevention of Subacute Bacterial Endocarditis

The preceding paragraphs give the clue to procedures which may prevent subacute bacterial endocarditis. Since rheumatic fever is the most common cause of the lesions upon which bacterial infection is later implanted, the prevention of that disease should head the list of our efforts. A detailed discussion of this important subject would take us too far afield; the reader is referred to the recent monograph by Rantz.[21] Recent developments in the prevention of rheumatic fever are also summarized by Hauser and Eckhardt.[22] It seems to be agreed that adequate penicillin treatment of group A streptococcal sore throats to the point of eliminating a carrier state cuts down greatly the subsequent occurrence of rheumatic fever. Children who tend to have recurring bouts may be helped by prophylactic doses of sulfadiazine or penicillin given continuously over months or years. Correction of certain congenital defects now possible by surgery will lessen the probability of implantation; ligation of patent ductus arteriosus and excision of areas of coarctation of the aorta can already be done, and no doubt repair of septal defects will soon be achieved by the surgeon. Unnecessary operations in regions which are common portals of entry should be shunned, especially in those with cardiac lesions. Tooth extraction and even rough dental manipulations (scaling) must, as far as possible, be avoided. However if such manipulation has to be done, prophylaxis with an appropriate antibiotic should be carried out. For tooth extraction we would suggest full doses of procaine penicillin (300,000 to 1,200,000 units daily in one or two intramuscular injections) given for one day before operation and for at least three or four days thereafter, depending on the clinical condition of the operative site. The studies of Glazer[19] and of Hirsh and their associates[22] show that penicillin does not sterilize the gums nor prevent bacteremia after tooth extraction but it may prevent implantation of streptococci or abort early infection. When urologic manipulations are done, penicillin and streptomycin can be used together, perhaps to advantage in preventing implantation of enterococci or other organisms not highly sensitive to penicillin alone. Aureomycin was found by Rothl and his associates[23] to reduce the incidence of

transient bacteremia which followed tooth pulling from 56 per cent to 4 per cent. They advise the administration of 0.5 Gm. every six hours, as the prophylactic of choice with dental extraction. However much remains to be done in this domain both as to choice of antibiotic and mode of administration.

Acute Bacterial Endocarditis

Diagnosis. In contrast to subacute bacterial endocarditis, which in the main is an entity of specific clinical and bacteriologic characteristics, acute bacterial endocarditis occurs as an incident in the course of any septic infection. The heart valves are not necessarily the seat of previous damage and no special bacterium is at fault. Acute bacterial endocarditis is, however, relatively frequent in severe infections with pyogenic cocci as well as with pneumococci and gonococci unless the primary disease is quickly controlled by antibiotic therapy.

Diagnosis, therefore, rests on one's alertness to suspect implication of the endocardium in every instance of septic infection whether it be a streptococcal sinus phlebitis, a colon bacillus pelvic infection, or multiple staphylococcal abscesses. The most valuable diagnostic data are the appearance of cardiac murmurs, especially if the clinical condition worsens with high irregular fever and chills, and persistent positive blood cultures usually with an increasing colony count.

Prevention of acute bacterial endocarditis hinges on the energy and resourcefulness of the physician. Appropriate surgery should be done promptly in threatening cases: opening and drainage of abscesses, ligation of infected venous sinuses, and similar procedures. Equally important is the early and intensive use of appropriate antibiotics in infections which offer a potential threat of endocardial implantation.

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ABSTRACTS

BACTERIAL ENDOCARDITIS

Dreyfuss, F., and Librach, G.: Cold Precipitable Serum Globulins ("Cold Fractions," "Cryoglobulins") in Subacute Bacterial Endocarditis. J. Lab. & Clin. Med. **40:** 489 (Oct.), 1952.

Cold precipitable globulins ("cold fractions" or "cryoglobulins") are found frequently in subacute bacterial endocarditis. Their presence was demonstrated in more than half (61.6 per cent) of the 180 serums examined in 50 cases of subacute bacterial endocarditis and only 8 of the 50 cases studied did not show such a globulin at any time during the observed course. Cold precipitable globulins are frequently associated with positive "dilution fraction tests" as well as with an increase in total globulin and euglobulin content of the serum. Forty-four of 55 determinations of serum globulin showed an increase in globulin content over 2.5 Gm. per cent.

The cold precipitable globulins have been found in a number of other conditions characterized by hyperglobulinemia, but in no disease state, except possibly in Kala-Azar, polyarteritis nodosa and multiple myeloma, have they been demonstrated in so high a proportion of cases.

The demonstration of cold precipitable globulins in the serum is technically a simple procedure and may occasionally be helpful in the diagnosis of subacute bacterial endocarditis before unequivocal clinical and bacteriologic evidence have been obtained.

MINTZ

BLOOD COAGULATION

O'Connor, W. R., Thompson, C. E., and Baker, L. A.: Experience with the New Anticoagulant Phenylindanedione in Acute Myocardial Infarction. Quart. Bull. Northwestern Univ. M. School **26:** 193 (Fall), 1952.

Phenylindanedione was employed to maintain a prothrombin deficiency in 50 cases of acute myocardial infarction. The recommended initial dose is 150 to 200 mg. A maintenance dose of 50 mg. twice daily will usually maintain blood prothrombin levels between 10 and 30 per cent of normal activity. Therapeutic levels of prothrombin deficiency are usually present in 16 to 40 hours. Prothrombin concentration returns to normal in 48 to 96 hours after the last dose of the drug. Individual dose requirement varied among patients. There were six deaths in this series for a mortality of 12 per cent. Two patients had a thromboembolism, an incidence of four per cent. Minor hemorrhagic manifestations occurred in three patients.

BERNSTEIN

Salvatore, S. A.: Capillary Fragility and Menstruation. Surg., Gynec. & Obst. **95:** 13 (July), 1952.

A capillary fragility test is often made in a patient with functional uterine bleeding as one of the studies necessary to establish a diagnosis of thrombocytopenia purpura hemorrhagica. This test is based on the appearance of petechiae. The author felt that there might be periodic variations of capillary fragility during the menstrual cycle in normal women. If so these would have to be taken into consideration in the evaluation of each test.

The method used was compression of the upper arm with a blood pressure cuff at medium arterial pressure maintained for three minutes. Then the petechiae below were counted. Studies were made on 60 women in both the intermenstrual period and during menstruation.

It was noted that during the first days of the menstrual period there was a slight increase in

capillary fragility as manifested by an increased number of petechiae in 78 per cent of the women.

FROBESE

CONGENITAL ANOMALIES

Bernreiter, M., and O'Connell, F.: Congenital Heart Block. J.A.M.A. **150:** 792 (Oct. 25), 1952.

Congenital heart block, an interesting and rare complication, is almost always associated with interventricular septal defect. In most cases this defect is in the membraneous portion of the interventricular septum. A case of irregular congenital heart block associated with septal defect and representing the syndrome of tetralogy of Fallot is reported. On the day of birth this was a three to one auriculoventricular block which changed to a two to one auriculoventricular block 14 days later. The child died after it was 14 months old and postmortem finding showed a moderately enlarged heart with a 15 mm. defect in the membraneous portion of the ventricular septum.

KITCHELL

Glenn, F., Keefer, E. B. C., Speer, D. S., and Dotter, C. T.: Coarctation of the Lower Thoracic and Abdominal Aorta Immediately Proximal to Celiac Axis. Surg., Gynec. & Obst. **94:** 561 (May), 1952.

A review of the literature indicates that congenital coarctation of the aorta in atypical sites is quite rare. When the constriction is in the lower thoracic and upper abdominal aortic region the usual surgical corrective measures of resection and end-to-end anastomosis or replacement by free arterial graft are not applicable because of the proximity of the celiac axis and other essential aortic branches in the abdomen. A cuff of aorta adjacent to these vessels suitable for anastomosis is not available. Therefore alternative procedures are required if the poor prognosis of the coarctation is to be improved.

A 19 year old white female was encountered with a congenital coarctation of the lower thoracic and abdominal aorta partially involving the celiac axis. The constriction revealed by angiocardiography and retrograde aortography measured 10.5 cm. in length and 0.5 cm. in diameter. The spleen was excised and the distal end of the splenic artery was anastomosed to the thoracic aorta proximal to the coarctated segment.

Postoperatively her symptoms were alleviated. Blood pressure in the arms and legs was equal and almost normotensive. Aortography revealed the blood flow through the splenic artery around the constricted segment into the celiac axis and the distal aorta. Oscillometric findings in the legs one year postoperatively were improved.

It was felt that this original operation would be of value in coarctation occurring in this unusual site. The blood supply distal to the stricture could be more than doubled by a very short operative procedure since only one anastomosis was required. Furthermore removal of the spleen might make more of the curtailed blood flow available to the intestines, liver, and kidneys.

FROBESE

CONGESTIVE HEART FAILURE

Fabre, J., Plattner, H. C., and Ducheskt-Maubetsch, A.: The Electrolyte Metabolism in Heart Failure. Exploration of the Intracellular Compartment. Arch. mal. coeur **45:** 903 (Oct.), 1952.

The authors report investigations on the metabolism and the balance of electrolytes in the course of development and treatment of congestive heart failure. During the onset of failure and formation of edema the blood level of sodium, potassium, chloride, nitrogen, calcium and phosphorus remains essentially unchanged. During excretion of massive edema there occurs a shift of extracellular sodium, and sometimes also potassium, into the cells. This is suggested by the observation that the excretion of chlorides exceeds by far that of the two cations, although the latter are found in equimolecular distribution with chloride in the edema fluid. Whether potassium or sodium is retained to a greater extent depends on dietary factors. Thus, a diet rich in potassium favors retention of this ion, while a mixed diet is followed by greater retention of sodium. The cause of this shift of electrolytes is not known, but the pH of the body fluids may play a role. The metabolism of other electrolytes (phosphorus, calcium and nitrogen) is not significantly altered by the presence of cardiac edema. However patients placed on a right protein-poor diet are apt to loose a considerable amount of cellular protein.

PICK

Weston, R. E., Escher, D. J. W., Grossman, J., and Leiter, L.: Mechanisms Contributing to Unresponsiveness to Mercurial Diuretics in Congestive Failure. J. Clin. Investigation **31:** 901 (Oct.), 1952.

The failure of cardiac patients to respond to mercurial diuretics probably is conditioned by many of the factors influencing salt and water retention in congestive failure. Detailed renal hemodynamic studies were performed in nine edematous and one edema-free cardiac patients who were maintained on a low salt diet and who were no longer responsive to mercurial diuretics despite digitalization, bedrest, and ammonium chloride. The increased diuretic response achieved by injecting 0.48 to 0.72 Gm. of theophylline ethylenediamine (aminophylline) intravenously, 90 to 120 minutes after the administration of a mercurial, was much greater than that observed following aminophylline alone and was associated with an increase in the severely impaired renal plasma flow, filtration rate, and filtered load of electrolytes The infusion of concentrated sodium

solutions intravenously 90 to 120 minutes after a mercurial led to an immediate increase in the diuresis in patients with reduced serum sodium and chloride concentrations. Evidence obtained from studies on desoxycorticosterone acetate suggests that adrenocortical activity may also contribute to mercurial resistance by increasing tubular reabsorption of sodium. The authors conclude that the failure of some cardiac patients to respond to mercurial diuretics is the result of the influence of many factors promoting sodium retention in congestive failure.

WAIFE

Covert, D. F.: Vitamin K Control of the Increased Hypoprothrombinemic Effect of Dicumarol in Congestive Heart Failure. Am. J. M. Sc. **224:** 439 (Oct.), 1952.

The pattern of response to Dicumarol of patients with congestive heart failure was evaluated by the Dicumarol tolerance test devised by the author in which the prothrombin response to a single 300 mg. dose is determined for three days. Compared to groups of normal subjects, the patients with congestive heart failure were found to have an increased susceptibility to the hypoprothrombinemic action of Dicumarol. The administration of vitamin K with Dicumarol reduced the effect of the latter agent in the cardiac group suggesting that vitamin K deficiency may be a factor in their increased susceptibility to Dicumarol.

SHUMAN

Davies, C. E., MacKinnon, J., and Platts, M. M.: Renal Circulation and Cardiac Output in "Low-output" Heart Failure and in Myxoedema. Brit. M. J. **2:** 595 (Sept. 13), 1952.

Patients with chronic rheumatic heart disease and with myxedema showed reduction in cardiac output, glomerular filtration rate, and renal blood flow of the same general degree. Yet the patients with myxedema, unlike those with rheumatic heart disease, tolerated large salt intakes without pitting edema. One patient with both myxedema and rheumatic heart disease had renal clearances of the same order as the other patients but was able to excrete salt and water normally. Although the cardiac output was low in both groups the myxedema group showed normal arteriovenous oxygen difference and normal cardiac output per unit of oxygen consumed. The authors theorize that the difference in the handling of salt results from a depression of tubular reabsorption in myxedema due either to local changes in the cell or to diminished hormonal stimuli from the adrenal.

MCKUSICK

CORONARY ARTERY DISEASE

Selzer, A.: The Hypotensive State Following Acute Myocardial Infarction. I. Clinical Observation. Am. Heart J. **44:** 1 (July), 1952.

In an attempt to study the pathogenesis of the hypotensive state associated with acute myocardial infarction the author studied 528 unselected cases of acute myocardial infarction. Sixty-nine patients had a shock-like state, and had a mortality of 70 per cent, in contrast to a mortality of 29 per cent for patients without shock. The author divided the sixty-nine cases into four classes on the basis of their course and clinical features. Group I consisted of 24 patients with immediate shock and precipitous fall in blood pressure. Signs of circulatory collapse cleared promptly either spontaneously, or in response to treatment of the initial attack of pain. Group II consisted of 28 patients who developed initially signs of circulatory collapse identical with those of group I, but persisted in shock until death. Group III consisted of nine patients with shock-like state coinciding with and apparently due to cardiac arrhythmias with extreme ranges of heart rate (complete atrioventricular block, paroxysmal ventricular tachycardia). Group IV consisted of 11 patients with hypotension which was not present upon admission, but developed gradually up to 36 hours after the onset. Three patients in group I and all in groups II to IV died. In groups I and II, the sudden fall in blood pressure coinciding with the attack of pain suggests that the shock-like state was initiated by a neurogenic reflex mechanism of some other peripheral mechanism affecting the venous return. In groups III and IV, large infarcts were present and the late shock which developed is considered to be a manifestation of irreversible cardiac failure of the "forward failure" type. Both peripheral and central factors play some part in each case. The dual origin of the hypotensive state should be considered in treating patients manifesting the shock-like state.

HELLERSTEIN

Selzer, A., and Taylor, G. W.: The Hypotensive State Following Acute Myocardial Infarction. II. Experimental Studies. Am. Heart J. **44:** 12 (July) 1952.

In order to evaluate the importance of peripheral and central factors in the pathogenesis of the hypotensive state following acute myocardial infarction, the authors studied the immediate effect of acute ligation of one and two main branches of the coronary arteries in dogs. The performance of the heart was tested by its response to an increased load produced by brief occlusion of the descending aorta in open chest dogs. In control dogs, aortic constriction produced an average rise of 57 mm. systolic pressure and 6 mm. diastolic pressure in the left ventricle. Following ligation of a branch of the left coronary artery, the performance of the left ventricle was found to be normal, comparable to control experiments, although slight elevation of the end diastolic pressure was frequently observed. Three dogs which survived the ligation of a second major

branch of the coronary artery developed true "cardiogenic" shock or hypotensive state characterized by systolic hypotension, elevation of end diastolic pressure in the left ventricle, failure of aortic constriction to produce an elevation of systolic pressure, and partially irreversible further elevation of the diastolic pressure brought on by aortic constriction. In dogs rendered hypotensive by extensive bleeding, the performance of the left ventricle following myocardial infarction was the same or even better than in normotensive dogs with myocardial infarction. Since hypotension was produced by the ligation of several coronary arteries, the authors state that hypotension associated with massive myocardial infarcts could be considered an example of true "cardiogenic" shocklike state in which the dilated left ventricle is unable to maintain an adequate output.

HELLERSTEIN

Block, Crumpacker, E. L., Dry, T. J., and Gage, R. P.: Prognosis of Angina Pectoris. J.A.M.A. **150:** 259 (Sept. 27), 1952.

Survival rates for 6,882 patients who had angina pectoris associated with coronary sclerosis and who were examined at the Mayo Clinic over a period of 18 years have been determined. The minimal follow-up period was five years and the maximal follow-up period was 23 years. Average age at diagnosis of angina pectoris was 58.8 years for the total series, 58.5 for the males and 60.1 years for the females. The ratio of males to females was roughly four to one, being highest in the younger age group and lowest in the older. Survival studies showed that mortality was greatest in the first year (about 15 per cent and that it was about 9 per cent per year thereafter. The survival curve for the series is decidedly lower than the curve for the normal population; the prognosis for females was better than for males. Five year survival rate for the entire series was 58.4 per cent as compared to the rate of 86.9 per cent for normal population. The 10 year survival rate of the series was 37.1 per cent as compared to the normal rate of 70.4 per cent. Cardiac enlargement, hypertension, myocardial infarction and congestive heart failure unfavorably influenced the prognosis. Those patients with angina pectoris and normal electrocardiograms as a group lived longest; those with significant alteration of T and Q waves had less favorable prognosis; and those with conduction disorders had the least favorable prognosis. Survival studies on patients with other conditions most commonly associated with angina pectoris included obesity, disease of the gall bladder, duodenal ulcer, thyroid disease, diabetes mellitus, and carcinoma. Angina pectoris associated with obesity alone carried the most favorable prognosis, and angina pectoris associated with carcinoma and diabetes mellitus carried the least favorable outlook.

KITCHELL

Aufdermaur, M.: Laceration and Thrombosis of a Coronary Artery Effected by Physical and Mental Stress. Schweiz. med. Wchnschr. **82:** 1086 (Oct.), 1952.

The author reports autopsy data on three cases in whom coronary thrombosis occurred under unusual circumstances. The first case was a 36 year old athlete who collapsed and died during a marathon run, just while passing the house of his parents. The second observation was a 66 year old policeman who, three days following a fight with a delinquent developed typical clinical signs of myocardial infarction and expired five days later. In the third instance sudden death occurred in the course of an uncomplicated tonsillectomy in a 36 year old man, subsequent to application of adrenaline.

The autopsy and histologic examination of the coronary arteries revealed similar findings in all three. There was narrowing of one of the coronaries. The thickened intima was torn in several places with consecutive hemorrhage into the vessel wall and subsequent thrombosis and complete occlusion of the lumen of the vessel. The author feels that the similarity of findings in these three cases may clarify the factors involved in sudden death under physical and/or mental stress. He also believes, that a similar mechanism, if not fatal, may initiate chronic coronary disease in otherwise healthy individuals, for instance young people undergoing repeated and strenuous sporting contests.

PICK

ELECTROCARDIOGRAPHY

Schaffer, A. I., and Beinfield, W. H.: The Vectorcardiogram of the Newborn Infant. Am. Heart J. **44:** 89 (July), 1952.

The authors studied vectorcardiograms of 35 newborn infants whose ages ranged from 3 hours to 7 days. The modified cube system of Sulzer and Duchosal was used. The patterns of the QRS loops were copied on paper from a Cambridge cardioscope. The spatial vector loop of the normal newborn infant is identical with that seen in older subjects with right ventricular preponderance. The initial part of the QRS loop proceeds anteriorly, superiorly, and usually to the right for a short distance. Then it swings downward, anteriorly, and slightly to the left, followed by a change of direction to the right, upward, and somewhat posteriorly. The terminal portion frequently lies to the right, superiorly, and posteriorly to the isoelectric spot. The direction was always clockwise in the frontal plane, clockwise in the horizontal plane in 33 of 35 cases, and clockwise in the sagittal plane in 27 of 35 cases. In two cases the neonatal loops were indicative of more marked right ventricular preponderance. Thus from a single electrocardiogram or vectorcardiogram, one cannot distinguish between normal and abnormal right preponderance during the first few weeks of life. If serial tracings show a persistence or an increase of

right preponderance the diagnosis of abnormal right preponderance is then justified. The authors discuss the distortion of the loops of the cube and other systems due to imperfections of the systems and the eccentricity of the neonatal heart.

HELLERSTEIN

Westlake, R. E., Sciess, W. A., Ershler, I. L., and Chiu, G. C.: The Effect of Digitoxin on the Electrocardiogram. Am. Heart J. **44:** 106 (July), 1952.

The authors studied the effect of oral digitoxin on the electrocardiograms of normal subjects. Digitoxin (1.2 mg.) was given to 40 normal subjects after a control tracing. An additional 0.4 mg. was given the next day to 22 of the subjects. Thirteen other subjects were given placebo tablets and the same routine followed. Control, 24-hour, and in the 22 subjects receiving the second dose, 48-hour tracings were taken. At 24 hours, the 40 digitalized normal subjects showed a significant decrease of heart rate of 5, shortening of Q-Tc of 0.019 seconds, and diminution of height of T-wave of 1.2 mm. Detectable S-T change occurred in only four subjects, none over 1.5 mm. At 48 hours, the 22 digitalized normal subjects showed further changes, the Q-Tc shortened 0.024 seconds, and T decreased 2 mm. in height. In the placebo treated subjects there was no statistically significant change in the electrocardiogram. The changes in S-T and T, as well as Q-Tc are explained by acceleration of repolarization of subendocardial muscle, thus abolishing the normal ventricular gradient. In normal hearts, digitoxin effect on repolarization is more predictable in the doses used, than it is on conductivity, rate, and rhythm.

HELLERSTEIN

Campbell, M., and Reynolds, G.: The Significance of the Direction of the P Wave in Dextrocardia and Isolated Laevocardia. Brit. Heart J. **14:** 481, 1952.

The authors determined the significance of the direction of the P wave in 40 instances. (1) 11 had dextrocardia with transposed viscera. Nine of the 11 had other congenital cardiac anomalies and seven of these were cyanotic. Nine had inverted P_1. One of the other two was investigated by angiocardiography and found to have a normally situated superior vena cava and right atrium. (2) Fifteen had isolated dextrocardia. All of these 15 had other congenital cardiac anomalies and 13 were cyanotic. Twelve of these 15 had upright P_1 waves. (3) Fourteen had isolated levocardia. All of these 14 had other congenital anomalies. Twelve were cyanotic. P_1 was inverted in six and P_2 and P_3 inverted in the other eight.

Upright P_1 is related to the normal position of the superior vena cava and right atrium. The side of the aortic arch gives some clue, but is less specific of the anatomic arrangements.

SOLOFF

Yu, P. N. G.: The Electrocardiographic Changes Associated with Hypercalcemia and Hypocalcemia. Am. J. M. Sc. **224:** 413 (Oct.), 1952.

Electrocardiograms and blood samples for calcium determination were obtained simultaneously on two patients with hypercalcemia and 10 patients with hypocalcemia. In hypercalcemia the Q-T interval and S-T segments were prolonged. These changes were most apparent in the left precordial leads and in the leads I and aV_L. They became apparent when the serum calcium fell below 7 mg. per 100 cc. The corrected Q-T interval was found to have a significant correlation with the serum calcium level. The author discusses the differentiation between hypercalcemia, digitalis effect and acute pericarditis as causes of shortened Q-T intervals. Similarly, hypopotassemia and quinidine, in addition to hypocalcemia, are presented as factors producing a prolongation of the Q-T interval. The electrocardiographic differentiation of each of these conditions affecting the Q-T interval is outlined.

SHUMAN

Heine, W. I., Sackett, C. F., and Serber, W.: Electrocardiographic Criteria of Left Ventricular Hypertrophy. Am. J. M. Sc. **224:** 424 (Oct.), 1952.

Cardiac evaluation of 1064 male veterans was conducted in an effort to appraise the specificity of the previously proposed criteria for left ventricular hypertrophy (LVH). Each patient was examined clinically, by teleoroentgenogram and by electrocardiogram. A roentgen-clinical classification of left ventricular hypertrophy was established. The correlation of these findings with the electrocardiographic diagnosis of left ventricular hypertrophy was then made, excluding from consideration those tracings in which the abnormality precluded evaluation of left ventricular hypertrophy.

The most sensitive criterion for left ventricular hypertrophy was found to be R of V_5 or V_6 + S of V_1 = more than 35, this being positive in 71 per cent of 149 cases showing left ventricular hypertrophy by the roentgen-clinical method. The criteria, $R_1 + S_3 = 25$ or more and RaV_L greater than 11, occurred only when the position of the heart was horizontal or semihorizontal. The time of the intrinsicoid deflection in V_5, V_6 showed the lowest sensitivity for left ventricular hypertrophy probably because of exclusion of cases with advanced changes.

The criterion based on precordial lead amplitude Rv5, 6 greater than 26 showed its highest correlation in patients with vertical hearts. The authors discuss the precautions which should be observed before any attempt should be made to use the electrocardiogram for the determination of left ventricular hypertrophy and indicate that occasionally,

normal individuals will show these manifestations.

SHUMAN

Eitel J., and Heintzen, P.: The P waves in Precordial Leads under Normal and Pathologic Conditions. Ztschr. Kreislaufforsch. **41:** 742 (Oct.), 1952.

In parasternal precordial leads, especially in V_1, certain alterations of the P wave can be found which suggest a deviation of the vector of auricular depolarization to the right and left and are supposed to indicate auricular pathology. These alterations were studied in 275 cases, 173 of which had no evidence of heart disease.

The change in contour of the P wave proved very variable and could not be correlated with the presence or absence of a so-called P mitral or pulmonale in the standard leads. Vectorial analysis revealed that alterations of the P waves in the precordial leads depends largely on the position of the electrode with reference to the level of the diaphragm. In addition it was found that enlargement of one or the other ventricles, with consequent rotation of the QRS vector to the left or right, may be associated with rotation of the P vector in the absence of any auricular pathology. The authors, therefore, conclude, that the appearance of an abnormal P wave in lead V_1 is of only limited value in the diagnosis of left or right auricular strain.

PICK

Popp, A: Application of Dorsal Thoracic Leads in Posterior Wall Infarct. Ztschr. Kreislaufforsch. **41:** 729 (Oct.), 1952.

In an attempt to amplify the diagnostic possibilities of myocardial infarction the author used, in addition to conventional leads the following chest leads: V_7, V_8, V_9 and a lead in the medioscapular line two finger breadths below the level of the diaphragm. The tracings were obtained in 100 cases several weeks after an attack of myocardial infarction, which involved in 30 instances mainly the anterior wall, and in the rest mainly the posterior wall.

In anterior wall infarction the additional leads did not contribute to the diagnosis which was evident from the customary chest leads. However, a deep Q wave and inverted T wave was seen in at least one of the dorsal leads in 67 of the 70 cases with posterior wall infarction, and this in the presence of a more or less normal precordial pattern. Technically the method proved simple and can be used without discomfort in bedridden and very ill patients. In view of its highly diagnostic value it should be preferred to other complicated procedures like esophageal leads used for the diagnosis of posterior wall infarct.

PICK

Bernstein, L. M., Pascale, L. R., Littman, A., and Foley, E. F.: Simultaneous Independent Paroxysmal Tachycardias. J.A.M.A. **150:** 446 (Oct. 4), 1952.

The occurrence of simultaneous independent paroxysmal tachycardias is regarded as extremely rare. This may be only apparently so owing to the difficulty of diagnosis because of superimposition of auricular complexes at a rapid rate on ventricular complexes. Seven patients are presented. In three cases the diagnosis is unequivocal being demonstrated electrocardiographically by conversion of paroxysmal auricular tachycardias to sinus rhythm without effect on the ventricular mechanism. In the other four cases the diagnosis was inferential, auricular flutter having been present immediately after and presumably during runs of ventricular tachycardia. Except for one patient with rheumatic heart disease (on whom cardiac catheterization was performed) all of these patients (age range 48 to 80) had definite evidence of advanced coronary artery disease with history of cardiac decompensation prior to the onset of the arrhythmias. It is believed that double tachycardias occur in the course of coronary artery disease and that they indicate a severe degree of heart disease. The recognition of two independent paroxysmal tachycardias is important in deciding what therapy is appropriate to slow the heart. It appears that the severity of the underlying heart disease will determine the final outcome.

KITCHELL

Harvey, W. P., and Levine, S. A.: Paroxysmal Ventricular Tachycardia Due to Emotion: J.A.M.A. **150:** 479 (Oct. 4), 1952.

"Frightened to death" is an expression which has been handed down generation after generation. In this article the authors discuss the possible mechanism of death from fright. A 29 year old noncardiac woman had volunteered for tests to study the effect of amyl nitrite on normal heart sounds and had been admitted to the hospital for this purpose. When it came her turn to be tested it was noted she was extremely apprehensive. During the preparation for the test she was connected to the electrocardiographic machine and the phonocardiograph. It was noted that a short burst of rapid beats occurred. Electrocardiographically these proved to be a short paroxysm of ventricular tachycardia. Inasmuch as this type of arrhythmia may be a prelude to ventricular fibrillation and death, it throws light on a possible mechanism of "death from fright."

KITCHELL

Gleckler, W. J., and Lay, J. V. M.: Wolff-Parkinson-White Syndrome and Paroxysmal Tachycardia in Infancy. J.A.M.A. **150:** 683 (Oct. 18), 1952.

The syndrome of anomalous atrioventricular excitation (Wolff-Parkinson-White syndrome) has been

reported in infants in only a few cases. This conduction defect seems to predispose the patient to attacks of paroxysmal tachycardia and such attacks are of a more serious nature in infants than they usually are in adults. A case is reported in a 4 month old infant whose attack of supraventricular tachycardia was successfully treated by intramuscular injection of lanatoside-C. The origin of the Wolff-Parkinson-White syndrome and its association with paroxysmal tachycardia are discussed briefly.

KITCHELL

Taimont, F., Carouso, G., Mege, A., and Lenegre, J.: Statistical Study on Bundle Branch Block. Arch. mal. coeur **45**: 926 (Oct.), 1952.

The authors studied the incidence of electrocardiograms with signs of defective intraventricular conduction in 6,132 consecutive cases. The various types of intraventricular block were correlated with clinical data, and with anatomic and histologic findings if these were available.

Right bundle branch block of the "rare" type was found only in cases with clinical and anatomic evidence of severe right heart involvement. The "S-type" of right bundle branch block appeared in about equal distribution among cases with right and left heart pathology, with a definite predilection for instances of arteriosclerotic cardiovascular disease. Incomplete right bundle branch block, with an R/S ratio greater than one in lead V_1 was found frequently in cases with right heart pathology, whereas a second type characterized by a small second R wave (r′) and a deep S wave in this lead, was divided equally among normals and cases with signs of right and/or left heart abnormalities. Three cases of incomplete right bundle branch block, who came to autopsy had a normal conduction system at histologic examination.

Complete left bundle branch block was found frequently in cases with involvement of both ventricles and only exceptionally in cases with right heart pathology, or without evidence of heart disease. In all instances examined histologically, a lesion was found in the left bundle. Incomplete left bundle branch block was found in about the same distribution, and frequently in cases with syphilitic heart disease. Histologic studies in six such cases confirmed the presence of lesions on the left side of the intraventricular conduction system.

PICK

HYPERTENSION

Moyer J. H., Tashnek, A. B., Miller, S. I., Snyder, H., and Bowman, R. O.: The Effects of Theophylline with Ethylenediamine (Aminophylline) and Caffeine on Cerebral Hemodynamics and Cerebrospinal Fluid Pressures in Patients with Hypertensive Headaches. Am. J. M. Sc. **224**: 377 (Oct.), 1952.

The effect of aminophylline and caffeine was studied in 13 patients with headaches of hypertensive origin. The relief of headache in all but two of the patients receiving each agent was frequently better than that obtained using opiates. Aminophylline proved superior to caffeine in affording relief. Measurements of cerebral blood flow by the nitrous oxide method disclosed an increase in cerebral-vascular resistance and a decrease in cerebral blood flow following aminophylline given intravenously. Caffeine produced similar changes but of lesser magnitude. Following each of these drugs the cerebrospinal fluid pressure decreased. The presence of renal disease or cardiac failure did not alter the responses noted. The data suggested that these agents decrease arterial and postarteriolar dilation of the cerebral vessels, thus relieving the headache produced by cerebral arterial distention in hypertension.

SHUMAN

Thomas, C. B.: The Heritage of Hypertension. Am. J. M. Sc. **224**: 367 (Oct.), 1952.

Analysis of the family history for hypertension and related disorders was conducted in a group of medical students. The diagnosis was based on information provided by the student or family physician. The incidence of hypertension in the parents of medical students was 25 per cent. The student subjects were studied for evidence of vascular lability which is the trait most often regarded as a precursor of hypertension. The determinants of circulatory lability were (a) high resting blood pressure, (b) high resting pulse rate, (c) transitory hypertension, (d) transitory tachycardia, (e) positive cold pressor test, (f) hyper-reactivity to excercise and (g) overweight. Although not every subject with parental hypertension showed evidence of vascular lability, the incidence of almost all of these traits was greater in the offspring of hypertensive parents. Thus 39.3 per cent of those with positive parental history showed evidence of circulatory lability compared with 15 per cent of the control group. Genetic studies suggest that hypertension behaves like a single recessive gene. Possibly hypertension bears an etiologic relationship to coronary artery disease; the same heritage is expressed more often as hypertension in females and as coronary artery disease in males.

SHUMAN

Browne, E. F., and Meyer, J. S.: Pheochromocytoma with Rupture of an Intracranial Aneurysm. Report of a Case. New England J. Med. **247**: 671 (Oct. 30), 1952.

The case of a man, aged 38 years, who died of a subarachnoid hemorrhage from a ruptured saccular aneurysm of the anterior communicating artery is described. There was also a meningocerebral hemor-

rhage in the right frontal lobe. The right adrenal gland was found to be largely replaced by soft encapsulated tumor, weighing 72 Gm. and having the typical histologic appearance of pheochromocytoma. The tumor contained a total of 113 mg. of norepinephrine and 129.6 mg. of epinephrine. The high norepinephrine content of these tumors is emphasized and it is pointed out that in situations such as this it is likely that constriction of the smaller cerebral vessels occurs during the paroxysms of hypertension. Such a situation is considered to elevate further the pressures within the larger cerebral vessels and favor rupture of a saccular aneurysm.

ROSENBAUM

Wilkinson, E. L., Backman, H., and Hecht, H. H.: Cardiovascular and Renal Adjustments to a Hypotensive Agent (1-hydrazinophthalazine: Ciba Ba-5968: Apresoline). J. Clin. Investigation **31:** 872 (Oct.), 1952.

1-Hydrazinophthalazine (Apresoline) was administered to normotensive and hypertensive subjects in single intravenous or intra-arterial doses of 0.25 to 0.5 mg. per kilogram of body weight. There was no consistent change in the systolic arterial pressure in the normotensive subjects, whereas the hypertensive group showed a fall averaging 66 mm. Hg, which was statistically significant. The diastolic pressure fell an average of 18 mm. in the normotensives and 50 mm. Hg in the hypertensive group. The maximum diastolic fall occurred in about 20 minutes and rarely returned to the control level within an hour, often not for two hours or more. Renal blood flow, as measured by para-aminohippurate, increased by an average of 40 per cent. This increased renal blood flow is more striking in the normal than in the patients with hypertension of heart disease. The total peripheral blood flow (cardiac output), as measured by oxygen consumption and A-V oxygen difference, increased by 110 per cent in the normal. This resulted in a relative decrease in the fraction of the total blood flow available to the kidneys.

There was no significant change in skin temperature following intravenous injections, although intra-arterially administered Apresoline caused a prompt and sustained rise in temperature of the involved extremity. A fall in arterial pressure in the face of an increased cardiac output must represent marked peripheral vascular relaxation. The authors conclude that this compound represents a potent selective vasodilator with properties resembling the vasodilator component of epinephrine.

WAIFE

Smirk, F. H.: Prolongation of Action of Hypotensive Drugs. Use of Polyvinyl-Pyrrolidone and Dextrans to Lengthen Effects of Hexamethonium and Hexamethylene Bis-ethyldimethylammonium. Lancet **2:** 695 (Oct. 11), 1952.

The hypotensive action of the two agents mentioned could be prolonged to five to seven hours by administration in polyvinyl-pyrrolidone or dextrans. Both menstrua have been used as plasma substitutes and are probably safe for this special use. A local vasoconstrictor (1/2000 ephedrine) resulted in further prolongation of hypotensive effects. Programs based on this information and combined sometimes with oral administration can provide smoother control of hypertension.

MCKUSICK

PATHOLOGIC PHYSIOLOGY

Agress, C. M., Rosenberg, M. J., Jacobs, H. I., Binder, M. J., Schneiderman, A., and Clark, W. G.: Protracted Shock in the Closed-Chest Dog Following Coronary Embolization with Graded Microspheres. Am. J. Physiol. **170:** 536 (Sept.), 1952.

The authors have described a method for producing emboli of the coronary arteries without opening the chest. The fall in blood pressure has been used as a criterion of coronary shock when reduction was 30 per cent or more of control values and did not rise for at least 30 minutes. Other criteria were electrocardiographic evidences of myocardial ischemia and evidence of severe myocardial damage at autopsy. The fall in blood pressure depends on the size of the emboli. By gravimetric and radioactive methods it is suggested that size and not number of vessels is the important factor in producing this kind of experimental shock.

OPPENHEIMER

Woolling, K. R., Allen, E. V., Roth, G. M., and Wakim, K. G.: A Method for Increasing Blood Flow to the Extremities by Simple Conservation of Body Heat: Preliminary Report of Effect of an Insulated Plastic Boot Applied to the Lower Extremities. Proc. Staff Meet., Mayo Clinic **27:** 393 (Oct.), 1952.

The application of a special plastic boot to the lower extremity produced an increase in the cutaneous temperature of the extremity, as measured by thermocouples, in each of 11 persons. The mean increase in temperature was 4.8 C. or 8.8 F.

Plethysmographic studies in another series of observations disclosed an increase in blood flow in the booted extremities of 7 of 11 persons. The mean increase in blood flow was 0.37 cc. per 100 cc. of tissue per minute, or 24 per cent more than the value observed under control conditions.

SIMON

Wright, H. P., Osborn, S. G., and Hayden, M.: Venous Velocity in Bedridden Medical Patients. Lancet **2:** 699 (Oct. 11), 1952.

Venous velocity in the legs was determined using $NaCl^{24}$ as a tracer. In 42 medical patients confined to bed for three weeks for noncardiac reasons, such

is peptic ulcer, no significant deviation from the normal was found. The comparison of hemiplegic limbs with the corresponding unaffected limb in 22 patients revealed greatly reduced venous velocity on the paralyzed side.

McKusick

King, B. D., Elder, J. D., and Dripps, R. D.: The Effect of the Intravenous Administration of Meperidine upon the Circulation of Man and upon the Circulatory Response to Tilt. Surg., Gynec. & Obst. **94:** 591 (May), 1952.

Studies were performed to determine the circulatory effects of Meperidine and to compare these results with those previously obtained after administration of morphine. These were made on 26 ambulatory human subjects ranging in age from 21 to 71 years.

It was deduced that the administration of Meperidine may decrease the ability of man to tolerate the circulatory stress of tilt, but that this was less likely to accur than the decrease following the use of morphine. Presumably the compensatory mechanisms of the circulatory system might be less able to combat shock or hemorrhage after use of either drug and marked hypotension could occur in patients with acute or chronic blood volume deficits even in the supine position.

There appeared to be very little additional danger to the administration of Meperidine by vein.

The possible causes for the circulatory effects were: (1) peripheral vasodilatation due to local liberation of histamine or due to central vasomotor depression and (2) diminished "respiratory pump" mechanism.

Frobese

Meyer, L. M., Berlin, N. I., Hyde, G. M., Parsons, R. J., and Whittington, B.: Changes in Blood Volume Following Administration of Dextran—Determined by P^{32} Labeled Red Cells. Surg., Gynec. & Obst. **94:** 712 (June), 1952.

Seven patients on the orthopedic service were selected for this study. All were hospitalized for fractures, but one had an associated cirrhosis of the liver. The initial blood volume of these patients was determined on two successive days utilizing P^{32} labeled red blood cells after the method of Hevesy and Zerahn.

Then 500 cc. of 6 per cent dextran was administered intravenously, and the blood volume of each was again determined. Three additional patients from the same service were used as controls and were similarly managed except that 500 cc. of physiologic saline was given in place of dextran.

In the control patients no significant changes in blood volume occurred. In six of the seven who received dextran the blood volume increased in amounts from 960 cc. to 2850 cc. The average increase was 1880 cc. The maximum increase occurred in one quarter hour to six and one-quarter hours after completion of the infusion.

The patient with cirrhosis had very little alteration of blood volume.

In the study, it seemed that the degree of response in the patients was related to the initial blood volume, but further observation would be necessary to confirm this point.

Frobese

Haynes, B. W., Jr., Crawford, E. S., and De Bakey, M. E.: Magnesium Metabolism in Surgical Patients: Exploratory Observations. Ann. Surg. **136:** 659 (Oct.), 1952.

The authors investigated the problem of magnesium metabolism in a group of surgical patients, pre- and postoperatively. Generally there was an initial retention of urinary magnesium which was followed by an increased excretion on the fifth postoperative day, these changes being paralleled by an early rise and a subsequent fall in the serum magnesium. The findings of an associated increased excretion of potassium and a retention of sodium suggested that a correlation existed between magnesium loss and adrenocortical activity.

Abramson

Peters, R. M., and Roos, A.: Effect of Unilateral Nitrogen Breathing upon Pulmonary Blood Flow. Am. J. Physiol. **171:** 250 (Oct.), 1952.

Dogs under morphine-chloralose and with open chests were the test objects. Most animals showed a 16 to 18 per cent reduction of the original fraction of total flow to the nitrogen lung. Oxygen reversed this result. Resistance increased 1.3 to 4.5 times in the nitrogen lung while the control oxygen lung was unchanged. Oxygen saturation of blood leaving the nitrogen lung was 10 to 50 per cent (8–25 mm. Hg oxygen tension) while mixed arterial blood was 62 to 96 per cent.

Oppenheimer

Green, J. P., Giarman, N. J., Salter, W. T.: Combined Effects of Calcium and Potassium on Contractility and Excitability of the Mammalian Myocardium. Am. J. Physiol. **171:** 174 (Oct.), 1952.

Contractility of papillary muscle of the cat depends upon ionic calcium concentration. In the physiologic range potassium does not influence contractility of this preparation but does decrease its excitability.

Oppenheimer

Brown, E. B., Jr., and Miller, F.: Tolerance of the Dog Heart to Carbon Dioxide. Am. J. Physiol. **170:** 550 (Sept.), 52.

During an hour to one and one half hours the carbon dioxide content of inspired air of anesthetized dogs was slowly increased up to 90 per cent. The blood pressure fell to zero and the heart was

arrested. The average pH at this time was 6.41. As carbon dioxide tension increased the heart rate gradually slows and P-R interval increases. At 60 to 65 per cent carbon dioxide respiratory arrest made artificial respiration necessary. The fall in blood pressure began at inspired concentrations of 50 to 70 per cent.

OPPENHEIMER

LeVoci, I. D., Bailone, S., Souza Paraiso, A. O., Ratto, O. R., Azevedo, E., and Molterno, E. A.: Hemodynamic Studies in Patients with Chronic Pulmonary Disease. Arq. brasil. cardiol. **5**: 235 (Sept.), 1952.

The authors report a study of the circulatory dynamics in 15 cases of chronic pulmonary disease with dominant signs of emphysema. Intracardiac catheterization was employed to determine cardiac output according to the Fick Principle, and to obtain records of the pulmonary artery and right ventricular pressures. The following conclusions were reached: (1) In the diagnosis of pulmonary emphysema, the clinical data, roentgenologic signs and the pulmonary function tests are of great importance and interest. (2) The level of the pulmonary arterial blood pressure is important to evaluate initial right ventricular strain in pulmonary disease. (3) Pulmonary hypertension after exercise, even when normal at rest, constitutes a sign of an abnormal pulmonary vascular bed. (4) The systolic pressure record in the right ventricle is similar to that of the pulmonary artery in chronic pulmonary disease. (5) Right ventricular diastolic hypertension is a characteristic sign of right heart failure. (6) The cardiac output is not uniformly altered in the course of pulmonary disease. (7) The cardiac output may be normal in the presence of mild right ventricular strain. (8) The cardiac output may be high in chronic pulmonary disease with right ventricular strain in the absence of myocardial damage. (9) The cardiac output is increased in chronic pulmonary disease with reversible right heart failure. (10) The cardiac output will attain normal values in the stage of myocardial involvement, decreasing still further in cases of irreversible heart failure.

SCHLESINGER

Tomlin, C. E., Logue, R. B., and Hurst, J. W.: Chronic Cor Pulmonale as a Complication of Fibrocystic Disease of the Pancreas. Am. Heart J. **44**: 42 (July), 1952.

The authors report two patients (20 and 27 months of age) with fibrocystic disease of the pancreas and chronic cor pulmonale secondary to chronic pulmonary disease. Clinical signs of right ventricular failure were present. Roentgenograms of the chest and electrocardiograms showed right ventricular hypertrophy. Both patients responded to mercurial diuretics, sodium restriction and digitalis administration, but died subsequently (the next day and nine months respectively) of the underlying disease. At autopsy hypertrophy and dilatation of the right atrium and ventricle were present. The authors state that although the benefit of therapy for congestive failure in cor pulmonale complicating fibrocystic disease of the pancreas may be limited, it should not be withheld or inadequately administered.

HELLERSTEIN

Breecher, G. A., Mixter, G., Jr., and Share, L.: Dynamics of Venous Collapse in Superior Vena Cava System. Am. J. Physiol. **171**: 194 (Oct.), 1952.

The studies presented deal with empyting and filling of extrathoracic veins during the respiratory cycle in dogs with intact chests. Inflow into the veins was from a constant pressure reservoir. Collapse during inspiration involves a segment of vein, not one point, in the extrathoracic vessels. This zone of collapse lies between noncollapsed intrathoracic veins and partially collapsed more peripheral extrathoracic veins. When volume is low, blood in the collapsing segment is reduced and as a result there is little or no increase of venous return in response to increased respiratory activity. On the other hand, when blood volume is large the collapsing transitional segment extends more into the periphery and as a result more blood is available to enter intrathoracic veins during breathing. If right atrial pressure is elevated the stage of depletion is longer and the beginning of collapse is delayed. When right atrial pressure does not descend below atmospheric, as in congestive failure, collapse does not occur and venous return depends on the extrathoracic-atrial pressure gradient. In experiments with the chest open it was shown that the reservoir of the extrathoracic veins acts as a collapse chamber and thus continuous venous flow is converted to a discontinuous one during breathing. It is pointed out that this provides a basis for understanding the mechanism of a net increase in venous return due to respiration.

OPPENHEIMER

PATHOLOGY

Waugh, D.: Myocarditis, Arteritis, and Focal Hepatic, Splenic and Renal Granulomas Apparently Due to Penicillin Sensitivity. Am. J. Path. **28**: 437 (May), 1952.

The writer records a case of granulomatous interstitial myocarditis, associated with exfoliative dermatitis and with other visceral involvements, which he believes was due to penicillin hypersensitivity. There was also focal arteritis, especially in the appendix, and marked eosinophilia, the latter appearing on resumption of penicillin therapy, previously used with indifferent success for pneumonia. The microphotography reveals eosinophilic and giant cell granulomatous myocarditis similar to

many cases which this reviewer recalls in the older literature under the name of Fiedler's interstitial myocarditis.

GOULEY

McLetchie, N. G. B.: The Pathogenesis of Atheroma. Am. J. Path. **28:** 413 (May), 1952.

The writer gives experimental support to the theory of Daguid (and Rokitansky) that atheroma has its genesis in the intimal accretion of thrombotic deposit, the engulfment of the latter by organization and the residual appearance of lipoid in the wake of disintegration and absorption of "red thrombi."

The author injected rabbits intravenously with a combination of Russell viper venom and bacto thromboplastin. This resulted in a more or less widespread thin thrombotic coating of the endothelial surface of the main branches of the pulmonary artery. Many rabbits received repeated injections over periods ranging from three weeks to seven months. It was noted especially after such repetition that mural endothelial thromboses were accompanied by thickening of the intima with fibroplastic proliferation of subendothelial mesenchyma. Endothelial proliferation grew over the mural coagula which eventually merged with the fibroplastic intima recognizable then as yellowish elevations. Microscopically these focal lesions consisted of conglutinated red cells degenerating into a mass of fatty material. The oldest lesions were organized to the point where they were comprised of fibro-fatty intimal elastosis. The latter suggests the additive factor of pulmonary hypertension.

McLetchie considers the difficulty of evaluating the differing theories of the pathogenesis of atheroma, but he believes that "thrombogenic atheroma" must receive serious attention, despite the fact that his findings are limited to the pulmonary circulation.

GOULEY

Block, W. J., Parker, R. L., and Edwards, J. E.: "Myxoma" of the Left Atrium Clinically Simulating Mitral Stenosis: Report of Case and Pathologic Studies. Proc. Staff. Meet., Mayo Clinic **27:** 361 (Sept.), 1952.

This report is based on a case of myxoma of the left atrium in which the patient was a woman aged 57 years. The clinical abnormalities suggested the diagnosis of mitral stenosis although a history of rheumatic fever could not be obtained and a diastolic murmur in the mitral area was heard only inconstantly.

Pathologically, the tumor lay in such a position as to obstruct the essentially normal orifice of the mitral valve. Supporting evidence for the opinion that the tumor had obstructed the orifice of the mitral valve includes the right ventricular hypertrophy and structural pulmonary vascular changes similar to those observed in cases of mitral stenosis and other conditions wherein there exists an impediment to pulmonary venous drainage. Coronary and cerebral embolism of tissue similar histologically to that of the left atrial tumor occurred. The position and nature of the tumor in this case support the opinion that a myxoma occurring in a cardiac atrium can be removed surgically.

SIMON

Loehr, W. M.: Pericardial Cysts. Am. J. Roentgenol. **68:** 584 (Oct.), 1952.

The author has made an extensive survey of the reported cases of pericardial cysts and has classified them on etiologic and pathologic bases. Congenital true cysts may be celomic (mesodermal), lymphangiomatous, bronchial cysts or teratomata. Acquired pericardial cysts may be secondary to hematoma, neoplasm or parasitic. True pericardial diverticuli and encapsulated pericardial exudate are classified as pseudo cysts.

A proved case of lymphagiomatous cyst of the pericardium is reported, successfully removed at operation. A second case with similar findings turned out to be a primary thymic tumor (lymphosarcoma). Four other cases showing cyst-like shadows inseparable from the heart-pericardial shadow, but not proved histologically are reported. Two of these were probably lymphatic cysts, the other two fulfilled the criteria of true diverticuli of the pericardium.

SCHWEDEL

PHARMACOLOGY

Mathes, S., Gold, H., Marsh, R., Greiner, T., Palumbo, F., Messoloff, C., and Perlmutter M.: Comparison of the Tolerance of Adults and Children to Digitoxin. J. A. M. A. **150:** 191 (Sept. 20), 1952.

Because digitalis therapy in children is the subject of much controversy, a study of 217 doses of digitalis administered to 71 adults and 170 doses administered to 54 children was made. During dosage 2,322 electrocardiograms were taken for analysis. Both adults and children received digitoxin orally on the basis of body weight, and each patient received an average of three doses, differing by 25 per cent. The effect that was measured was the percentage of patients showing a change of the RS-T segment of the electrocardiogram. Comparison and results showed that, when the dose is calculated on the basis of body weight, children require about 50 per cent more digitoxin by oral administration than adults, for the production of a similar effect.

KITCHELL

Texter, E. C. Jr., Redisch, W., Sheckman, E., Ferguson, S., and Steele, J. M.: Evaluation of Vasodilator Drugs in Four Patients with Arteriosclerosis Obliterans. Am. J. M. Sc. **224:** 408 (Oct.), 1952.

The vasodilating properties of four drugs (a) Pronestyl, (b) Roniacol, (c) Priscoline and (d) SKF 688A (a dibenamine ester) were assayed on four patients with clinical signs of arteriosclerosis obliterans. These drugs and placebos were administered orally for 15 days in divided doses. Intravenous administration was used in a few instances. Evaluation of drug effectiveness was based on claudication time using a bicycle ergometer, skin temperature responses and the evidence of night cramps and intermittent claudication. Side effects were those of gastric irritation and anorexia, occasionally, with each of the drugs and flushing of the face with Roniacol. Pronestyl was found to have no vasodilating effect. Roniacol improved intermittent claudication while Priscoline was most effective in relief of night cramps. SKF 688A showed vasodilating properties; however, this agent caused blurring of vision and fixed pupillary constriction. Because of the lack of agreement among the various criteria, it was concluded that multiple tests were required for the evaluation of the vasodilator effects of drugs.

SHUMAN

Kuehns, K.: Hydrergin Therapy in Cases with Impairment of Coronary Circulation and with Cardiac Heterotopias. Ztschr. Kreislaufforsch. **41:** 721 (Oct.), 1952.

The author used oral and intravenous Hydrergin, a complex of purified ergot alkaloids, for the treatment of angina pectoris and of cardiac irregularities.

Among 59 cases of angina so treated the response was excellent in seven with respect to intensity and number of attacks. In 25 cases a definite improvement of the clinical symptoms could be noted, and in 7 per cent of the cases improvement of electrocardiographic alterations. The best results were observed in cases in which chest pain occurred in association with hypertension or valvular disease. However, in the treatment of the acute anginal attack Hydrergin proved inferior to nitroglycerin. It was of no value in treatment of pain due to myocardial infarction.

The effect of the therapy with Hydrergin on various types of disturbances of rhythm was studied in 28 cases, and in part of them compared with the effect of quinidine. There was a definite improvement of subjective symptoms and of the frequency of premature beats in eight cases. In 13 instances with auricular fibrillation associated with a rapid ventricular rate subjective sensations like palpitations, headache and vertigo were definitely improved but the drug remained without effect on the disturbance of rhythm. However, in three cases who suffered from paroxysmal auricular fibrillation the frequency of attacks could be reduced.

PICK

Marsh, R., Greiner, T., Gold, H., Mathes, S., Palumbo, F., Warshau, L., and Weaver, J.: A Comparison of the Diuretic Effects of Mercuhydrin (Meralluride) Administered by Several Routes. New England J. Med. **247:** 593 (Oct. 16), 1952.

The effectiveness of Mercuhydrin by intravenous, intramuscular, subcutaneous, rectal and oral routes was determined. The method for bioassay of diuretic agents described by Greiner and colleagues was employed. His plan provides for the use of Mercuhydrin by intramuscular injection as the standard against which other drugs or the same drug by other routes of administration is compared. The measure of response is the loss of body weight in the 24 hours after the dose. Forty-nine ambulant patients with various forms of heart disease associated with moderate to moderately severe congestive heart failure were used in these assays. There was no significant difference in the potency of Mercuhydrin when given by intravenous, intramuscular or subcutaneous injection. The attempt to assay its effectiveness in the form of rectal suppositories was unsuccessful since the suppository was often poorly retained and absorption was uncertain. The data obtained suggested that Mercuhydrin was only about 7 per cent as effective by this route as by the intramuscular route. When given by the oral route the drug had only 4 per cent of the potency of the material given intramuscularly. The major part of the diuretic action of a single dose of the drug given orally appeared to take place in the first 25 hours. The addition of ascorbic acid did not appear to enhance the action of orally administered Mercuhydrin, nor did it reduce the local irritant action of the organic mercurial. Neither did the use of Mercuhydrin Sodium in the form of a solution reduce the frequency of gastrointestinal irritation.

ROSENBAUM

Hoffman, I., Abernathy, R. S., and Haedicke, T. A.: Effect of Procaine Amide on Anomalous Conduction and Paroxysmal Tachycardia in a Case Resembling the Wolff-Parkinson-White Syndrome. Am. Heart J. **44:** 154 (July), 1952.

The authors studied a 35 year old soldier with recurrent paroxysmal tachycardia. Upon admission to the hospital, the patient had nodal tachycardia with a rate of 188. After six hours of sustained tachycardia, the patient was given 1 Gm. of procaine amide orally. Twenty minutes later there was a sudden conversion to a regular sinus rhythm with a rate of 84, P-R interval of 0.16 second and QRS complexes of 0.08 second duration. The QRS complexes were of similar configuration to those recorded during the paroxysm. Serial records revealed that an alternate cardiac mechanism occurred spontaneously and intermittently, in which the P-R interval was shorter (0.12 to 0.13 second), and the

QRS complexes were wider (0.10 to 0.11 second) than in periods with normal conduction. A single dose (1 Gm.) of procaine amide by mouth would eliminate the aberrant conduction for about 12 hours. This case is not typical of the Wolff-Parkinson-White syndrome, in that the P-R interval is longer and the QRS duration is shorter. To account for the somewhat shortened P-R interval and the nodal, rather than ventricular, character of the QRS complexes, the authors suggest that an alternate pathway exists, bypassing part, but not all of the atrioventricular node.

HELLERSTEIN

PHYSICAL SIGNS

Edwards, E. A., and Levine, H. D.: The Murmur of Peripheral Arteriovenous Fistula. New England J. Med. **247:** 502 (Oct. 2), 1952.

The murmurs heard over peripheral arteriovenous fistulas are high-pitched and continuous with systolic accentuation. The systolic accentuation may be exaggerated or the murmur converted into a systolic one by compression of the effluent vein. The intensity of the murmur is said to be roughly proportionate to the size of the fistula although minute fistulas may be present without a murmur. The murmur is most intense over the site of the fistula but it may be widely transmitted along the vein leading out of the fistula and via the bones. Bone transmission is said to be particularly helpful in the diagnosis of intracranial fistula. The mechanisms of murmur production in this disorder are said to include increase in velocity of the blood stream and abrupt changes in vessel diameter. The higher gradient of pressure during systole accounts for the systolic accentuation of the murmur and the reduction of this gradient by venous obstruction decreases or eliminates the diastolic element of the murmur. Murmurs of this type must be differentiated from murmurs of cardiac origin, from venous hums which are also continuous but with a diastolic accentuation, from systolic murmurs due to partial intrinsic or extrinsic obstruction of arteries and from those associated with arterial aneurysm.

ROSENBAUM

Sloan, A. W., Campbell, F. W., and Henderson, A. S.: Incidence of the Physiologic Third Heart Sound. Brit. Med. J. **2:** 853 (Oct. 18), 1952.

In a group of 123 Glasgow University students, aged 17 to 32 years, without evidence of heart disease, a third heart sound was heard by a majority of three observers in only 9.8 per cent. Deflections in the position of the third sound were recorded in linear and stethoscopic phonocardiograms of 100 per cent of subjects and in logarithmic phonocardiograms of 39 per cent.

MCKUSICK

Palfrey, F. W.: A Practical Aid in the Detection of Cardiac Hypertrophy. New England J. Med. **247:** 612 (Oct. 16), 1952.

A technic is described for determining heart size by auscultation. It is suggested that the stethoscope be placed over the fifth left cartilage near the sternum and then moved horizontally outward, 1 cm. at a time, toward the left axilla. A sudden, quite marked lessening in the loudness of both sounds is said to occur at a point which corresponds closely to the left border of cardiac dullness in mid-respiration as determined by expert percussion. If this point is within the midclavicular line, both enlargement and displacement to the left are excluded. The right border and the upper border of the heart may be determined similarly. It must be made certain that there is not further extension of the left border in the fifth space or under the sixth rib from downward enlargement. The center rather than the edge of the end-piece of the stethoscope is said to mark the point of significant loss of loudness.

ROSENBAUM

SURGERY IN HEART AND VASCULAR SYSTEM

Gross, A. E., Pomeranz, A. A., Watkins, E., Jr., and Goldsmith, E. I.: Surgical Closure of Defects of the Interauricular Septum by Use of an Atrial Well. New England J. Med. **247:** (Sept. 25), 1952.

Gross and his associates have developed a technic employing a cone-shaped rubber bag attached to the right auricular wall through which an opening is made into the auricle allowing the blood to rise up into the rubber well. The operator can work through this column of blood, explore the septum and close any opening present by direct suture or the onlay of a piece of flat material such as pericardium, fascia or plastic. A series of 114 dogs were used to develop proper technics for attaching the rubber well to the auricle, selecting the proper type of well and devising a self-retaining retractor to keep open the orifice in the lateral wall of the auricle. In these experiments it was found that the necessary manipulations of the auricle did not produce significant auricular arrhythmias or alter the pulse rate. The blood rose to a level of four to eight cm. in the well, varying one or two cm. with respiration. Air was not sucked into the auricle, the peripheral blood pressure was adequate and the well could be left open for periods up to one hour and yet a stable circulation was maintained. The technics of closure of septal defects employed in these experiments included (1) free grafts of pericardium, (2) free grafts of pieces of vein, (3) free grafts of the tip of the right auricular appendage, (4) application of Hufnagel two-disk button prostheses, (5) application of sheets of plastic material, and (6) direct closure by use of interrupted silk sutures.

The clinical application of these technics in six patients is reported. The rubber well used in humans had a height of 15 cm., an upper-orifice diameter of 13 cm. and a lower-orifice diameter of 4 cm. The six patients ranged in age from 4 to 16 years. Preoperative studies disclosed shunts ranging from 6.7 to 22.3 liters per minute. The blood in the well was kept fluid by regional heparinization. In one case the well was kept open for two hours and five minutes. Double buttons of the Hufnagel type were used in the first three cases; all ended disastrously because the buttons worked loose. A plastic plate used in the fourth case was too large and was not anchored sufficiently so that clot forming about it obstructed the orifice of the tricuspid valve. A nylon plate was used to close a septal opening 2 cm. by 3 cm. in size in the fifth case; this patient was in excellent condition and had no murmur two months postoperatively. The sixth patient had two septal defects, 1.5 cm. by 10 cm. and 3.5 by 1.0 cm. in size, each of which was closed by direct suturing and approximation of the septal margins; this patient was also in good condition and had no murmurs two months postoperatively.

ROSENBAUM

Brock, R. C.: The Surgical and Pathological Anatomy of the Mitral Valve. Brit. Heart J. **14:** 489 (Oct.), 1952.

Based upon observation on many normal and diseased specimens and direct study of the valve at some 150 operations, Brock believes that much that is now taught of the normal and diseased mitral valve is unacceptable.

He states that the valve mechanism normally extends over a distance of about 5 cm. It consists of two cusps, the anteromedial that is larger and more important and posterolateral that is a secondary and supporting part. The two papillary muscles that lie opposite the interval between the valve cusps arise from the ventricular wall at the junction of the apical and middle thirds. The chordae tendineae arise from these muscles one set controlling the anterolateral and the other the posterolateral half of the valve. The critical areas of tendon insertion are two on each cusp about 2 cm. apart at the function of the horizontal and lateral receding parts of the valve cusps. The cusps are driven together by the rise in pressure during ventricular systole and are prevented from being blown open into the atrium by tensing of the chordae tendineae.

At operation, Brock has found the mitral orifice in stenosis almost always a small oval about 1 cm. by 0.5 cm. According to him, there may be little difference in the size of the orifice in patients with mild or severe symptoms. This is because mitral stenosis is due, fundamentally, to fusion of the valve cusps at the two opposing critical areas of tendon insertion. Lateral to this fusion, the valve is functionless. The orifice may become smaller due to the deposition of platelets, fibrin, fibrous and even calcified plaques. Later the chordae tendineae become fibrous. Severe mitral obstruction can, therefore, occur in the presence of mild valvulitis.

In the severe forms of rheumatic valvulitis, the process spreads to the cusps, chordae tendinae, A-V ring and even papillary muscles. This effect may prevent relief of mitral obstruction by commissurotomy.

Mitral regurgitation may be due to (1) defect in cusp, (2) rigidity of margins of valve, (3) rupture of musculotendinous mechanism, (4) shortening of one or both cusps, (5) shortening of musculotendinous mechanism, and (6) dilatation of atrioventricular ring.

In mitral incompetence found at operation, Brock has observed three forms (1) small regurgitant stream from a small, stenosed valve (2) moderately powerful regurgitant stream from a slightly stenosed valve (3) powerful regurgitant stream without stenosis. Type one is of no importance. Type two represents the most severe grades of damage to the valve by rheumatic infection. There is involvement of the total valve and papillary muscles. Type three is found with a large left ventricle and left atrium.

SOLOFF

Thiessen, N. W., and Marxen, N. L.: Successful Direct Aortic Embolectomy. Am. J. Surg. **84:** 358 (Sept.), 1952.

A case is described of a 57 year old female with atrial fibrillation who developed complete occlusion at the bifurcation of the aorta as a result of an embolus. Within three hours after the onset of the condition, direct aortotomy was performed for removal of the embolus. At the same time a small clot was also found in the right iliac artery.

Following surgery, a therapeutic spinal anesthesia was administered and anticoagulants were given. An area of gangrene appeared on the tip of the right great toe and a foot drop developed in the right foot. However, the patient recovered from these complications and 27 months after embolectomy, she was living and well.

ABRAMSON

Julian, O. C., Dye, W. S., Olwin, J. H., and Jordan, P. H.: Direct Surgery of Arteriosclerosis. Ann. Surg. **136:** 459 (Sept.), 1952.

The authors present their results using vein grafts and intimectomy in a series of 26 patients with arteriosclerosis obliterans. In the selection of cases, arteriography was relied upon for the determination of whether or not segmental thrombosis existed and also for the site of occlusion.

In 18 patients 19 vein grafts were used to replace segments of the superficial femoral artery. In 16 instances the portions of veins were autografts taken from superficial femoral or saphenous veins, while in three, saphenous hemografts were used. Twelve of

the 19 grafts were successful in restoring the circulation, as evidenced by a return of pulses in the foot and relief of intermittent claudication. The remaining seven cases were failures.

Six patients were subjected to intimectomy; in five this was performed in the iliac artery and in one in the superficial femoral artery. Four of the operations were considered to be successful, while in the remaining two reocclusion of the segment occurred.

The authors concluded that both procedures have definite limitations and are of use only as temporary measures. In most instances, even after removal of the occluded portion, there is still arteriosclerotic involvement of the remainder of the arterial tree, this change being conducive to future obstruction.

ABRAMSON

Muller, W. H., Jr., and Dammann, J. F., Jr.: The Surgical Significance of Pulmonary Hypertension. Ann. Surg. **136:** 495 (Sept.), 1952.

The authors present evidence indicating that pulmonary stenosis should be produced surgically in those patients in whom a low pulmonary resistance and cardiac failure develop. It is their belief that the partial obstruction in the pulmonary artery would reduce the pulmonary blood flow and pressure distal to the obstruction and at the same time increase the systemic and coronary artery blood flow.

They are also of the opinion that pulmonary stenosis should be induced in those cases in which pulmonary vascular resistance is high due to medial hypertrophy, with or without a moderate amount of intimal fibrosis. They considered the possibility that with a reduction in pulmonary artery pressure, there might be a decrease in the changes in the muscle layer of the vessels. They believe that an extreme degree of intimal fibrosis was a contraindication to the operation unless it could be demonstrated that this process was reversible.

ABRAMSON

Spiegl, R. J., Long, J. B., and Dexter, L.: Clinical Observations in Patients Undergoing Finger Fracture Mitral Valvuloplasty. 1. Auscultatory Changes. 2. Electrocardiographic Observations. Am. J. Med. **12:** 626 (June), 1952.

Following finger fracture mitral valvuloplasty in 18 patients with mitral stenosis of rheumatic origin, a significant decrease in the intensity and duration of the apical diastolic murmur occurred in patients who improved after the operation. This decrease in the apical mitral systolic murmur was the best clinical index of expected postoperative improvement. Its absence or the development of an operative apical systolic murmur of grade 3 intensity or greater was generally prognostic of a poor postoperative result. A Graham-Steell murmur, indicative of pulmonic insufficiency, was present in six instances and disappeared postoperatively in all. The loss of this murmur is a more sensitive index of decreased pressures within the pulmonary arterial circuit than the altered P^2. The loud snapping apical first sound heard in mitral stenosis was changed little by the operation.

Continuous electrocardiographic recordings throughout the entire procedure disclosed the transient occurrence of a great variety of cardiac arrhythmias at different stages of the operation. The authors discuss the indications, dosage and effect of some readily available drugs for the treatment of these arrhythmias. Prostigmin has proved useful in all supraventricular tachycardias because of its marked vagotonic effect. Pronestyl was efficacious in the treatment of ventricular ectopic beats and ventricular tachycardias. Atropine and procaine were also useful. The former was of help in marked bradycardias and the latter in the suppression of ventricular ectopic beats induced by manipulation of the heart.

HARRIS

Coehlo, E., Fonseca, J. M., Nunes, A., and Barros, F.: The Importance of Physiopathologic Studies in Mitral Stenosis for the Indication to Commissurotomy. Cardiologia **21:** 626 (Fasc. 4/5), 1952.

A study of the cardiovascular dynamics in 46 cases of mitral stenosis is reported including recordings of pulmonary pressures and calculations of right ventricular output, pulmonary vascular resistance and of the degree of valvular constriction. The hemodynamic data were compared with the clinical symptoms and electrocardiographic, radiographic and angiocardiographic findings. The material was classified into five groups.

The first "benign" group consisted of cases with typical physical findings of mitral stenosis without evidence of right ventricular hypertrophy or pulmonary hypertension, a normal cardiac output at rest and an adequate increase on exercise. In a second group cases were included with a normal sized heart in the presence of pulmonary hypertension and increased pulmonary vascular resistance. A third group was represented by cases with enlargement of the right heart and pulmonary arteries and a more marked pulmonary hypertension. In group four there were similar cases with frequent attacks of pulmonary edema or hemoptysis and roentgenologic signs of hemosiderosis. Finally in a fifth group all these signs were associated with progressive right ventricular failure.

From the surgical standpoint only in group II commissurotomy is absolutely indicated. In groups III and IV, changes in the pulmonary vascular tree may be so far progressed that a benefit from the operation cannot always be expected. Groups I and V are considered not suitable for surgery.

PICK

Lian, C.: Surgical Creation of an Arterio-Venous Fistula with Ligation of the Subjacent Vein as Treatment of Severe and Persistent Arterial Hypertension. Cardiologia **21:** 347 (Fasc. 4/5), 1952.

In view of unsatisfactory results of extensive sympathectomy the author previously suggested the formation of a femoral arteriovenous fistula in order to relieve severe arterial hypertension. The operation was initially performed on seven patients but frequently was followed by development or aggravation of heart failure. Subsequently the operation was performed in a group of nine patients with additional ligation of the femoral vein above the fistula. In two cases the same operation was done in the axillary instead of the femoral region. The results in this group are reported as excellent. There was a definite improvement of symptoms, the systolic pressure fell in the average by 30 mm. and the diastolic by 20 mm. In cases operated on by this improved technic heart failure did not develop, and if preexistent, improved. There was no mortality which could be attributed to the surgical procedure.

The author considers the creation of an arteriovenous fistula indicated in all cases of hypertension, in whom the diastolic pressure is 140 mm. or more, who have no evidence of renal failure and are in good general condition. It is likewise indicated in patients with diastolic pressures of 120 to 130, if marked symptoms like headache and dizziness are present.

PICK

Fischer, H. W., Albert, H., Riker, W. L., and Potts, W. J.: Successful Experimental Maintenance of Life by Homologous Lungs and Mechanical Heart. Ann. Surg. **136:** 475 (Sept.), 1952.

Experiments were performed on dogs to show that life could be maintained by the use of homologous lungs and mechanical circulation, while the heart and lungs of the animal being studied were excluded from the general circulation. Two Dale-Schuster pumps were substituted for the right and left ventricles. The dogs which supplied the homologous lungs were anesthetized and exsanguinated.

Since it was found that animals subjected to the procedure survived and remained in good health, it was concluded that homologous lungs could serve as a satisfactory mechanism for the respiratory exchange of gases.

ABRAMSON

THROMBOEMBOLIC PHENOMENA

Samuels, P. B., and Webster, D. R.: The Role of Venous Endothelium in the Inception of Thrombosis. Ann. Surg. **136:** 422 (Sept.), 1952.

The authors studied the venous endothelium of dogs, using new technics which allowed permanent preparations to be made and which demonstrated the histologic structure of this tissue. Through the application of various types of noxious stimuli, they were able to follow the sequence of events that led up to venous thrombosis.

The earliest change was adherence of platelets to the cement substance of the wall, these coalescing to form platelet thrombi. The next step was the deposition of fibrin on the surface of the thrombi, the fibrin masses then spreading along the intercellular lines and across the cell bodies.

If the initial injury was severe or long continued a maximal reaction occurred. This involved a disruption of the continuity of the endothelial surface and pathologic changes in the endothelial cells consisting of the appearance of intracellular granules and lightly-staining nuclei. Small separations took place in the intercellular lines and desquamation of the endothelium of the wall was noted. Fibrin was then deposited in the involved sites.

The preliminary use of heparin prevented deposition of platelets on the intercellular cement of the normal vein wall, but it had no effect on inhibiting the process of local thrombosis in the presence of injured endothelium.

ABRAMSON

Ebel, A., Kaufman, M., and Ehrenreich, T.: Gangrene of an Extremity Secondary to Venous Thrombosis. Arch. Int. Med. **90:** 402 (Sept.), 1952.

Massive venous occlusion of the left lower extremity resulted in gangrene of the foot in a case of adenocarcinoma of the pancreas. The occlusion was due to phlebothrombosis of the entire venous system from the iliac to the dorsalis pedis veins. The corresponding arteries were patent. The immediate cause of death was massive pulmonary embolism which occurred notwithstanding anticoagulant therapy. The characteristic symptoms which should lead one to suspect this condition are extensive edema, usually involving the entire extremity, associated with blanching of the skin in the early phases followed rapidly by blue discoloration, coldness, and severe pain that may be sudden in onset or progressive. Arterial pulses are palpable in about one-third of the patients, while in the remaining two-thirds the distal arterial pulsations cannot be felt. The disappearance of pulses may be caused by the extensive edema or may be the result of the secondary arterial spasm which is frequently associated with thrombophlebitis. However, the experience of most observers that vasodilator drugs, as well as autonomic nerve blocks, are of little therapeutic value would lead one to conclude that vasoconstriction plays a relatively insignificant role in the abolition of the arterial pulsations.

The treatment is quite unsatisfactory. Sympathetic nerve blocks and vasodilator drugs have not been found to be of great value. Anticoagulant therapy has no effect on the already established venous obstruction and, thus, is not useful in the treatment of the gangrene until blood flow has been reestab-

lished by one means or another, if such reestablishment is at all possible. However, anticoagulants may be of value in preventing propagation of the thrombus proximally and in reducing the likelihood of pulmonary embolization. Amputation remains the only recourse in cases of extensive gangrene.

BERNSTEIN

Musgrave, J. E., and MacQuigg, R. E.: Successful Treatment of Air Embolism. J.A.M.A. **150:** 28 (Sept. 6), 1952.

The excellent experimental work published by Durant, Long and Oppenheimer in 1947, plus the discussion of a case treated by Hamby and Terry, made it possible for the authors to properly manage a case of severe air embolism by turning the patient to the left lateral position. It is hoped that this additional report will draw the attention of others to the fact that air embolism can be treated successfully by this simple maneuver.

KITCHELL

VASCULAR DISEASE

Hoff, H. E.: Physiologic Problems in Peripheral Vascular Disease. Anesthesiology **13:** 474 (Sept.), 1952.

The author presents a discussion of the problem of the function of peripheral vessels acting as supply lines to a peripheral structure. By determining changes that occur in the function of a vessel—color and temperature changes of a limb, alterations in the blood flow through a limb, pallor, cyanosis and trophic changes—we can infer that changes have occurred in a vessel. The reactions of blood vessels to thermal changes and mechanical trauma encompass the entire range of normal and pathologic reactions and offer a fertile field for study.

Exposure of the limbs of a normal subject to cold results in slowing of the blood flow through the digits but not in arterial closure. In Raynaud's disease and allied conditions closure appears for varying periods of time. Raynaud believed that in this disease excessive activity of the sympathetic vasoconstrictor fibers led to a spasm of the peripheral vessels. Other studies, however, indicate that the basic difficulty in Raynaud's disease may be primarily vascular in origin and not sympathetic and results from an altered responsiveness of the blood vessel to the stimulus of cold. Evidence and arguments for this concept are reviewed and discussed.

The problems of recovery of function after sympathectomy is considered. In many patients the early and marked improvement in circulation to the extremities found after sympathectomy is not maintained and sympathetic activity returns to a variable degree. Several possible explanations for this phenomenon are discussed: (1) The operative procedures presently used may not completely denervate the part involved, particularly the upper extremity, so that sympathetic activity returns after the local shock effect of operation via residual sympathetic pathways. (2) After preganglionic section of the upper limb the intact preganglionic fibers in the first thoracic white ramus communicans may form new synaptic connections with cells in the cervicothoracic ganglia and thereby innervate the upper limbs. (3) Local peripheral reflex centers may be active. (4) After sympathectomy the divided sympathetic fibers may regenerate and reconnect with residual ganglia. (5) Degenerations of the postganglionic neurons following operation may result in hypersensitization of the denervated vessels to circulating epinephrine. Evidence for the above hypotheses is discussed but the problem has not been solved.

SAGALL

Bean, W. B., and Mohaupt, F. X.: Rupture of the Aortic Valve. J.A.M.A. **150:** 92 (Sept.), 1952.

The literature regarding rupture of the aortic valve is reviewed and a case is reported. The signs seen in the present case were those of severe aortic regurgitation with severe persistent cough and progressing heart failure which responded poorly to therapy. Death occurred in four months. It is suggested that this type of lesion should be correctible by surgical operation.

KITCHELL

OTHER SUBJECTS

Harned, H. S., Lurie, P. R., Crothers, C. H., and Whittemore, R.: Use of the Whole Blood Oximeter During Cardiac Catheterization. J. Lab. & Clin. Med. **40:** 445 (Sept.), 1952.

The purpose of this study was to evaluate the accuracy of the cuvette or whole blood oximeter in measuring oxygen saturation values and to evaluate the oximeter as an aid to the operator at the time of cardiac catheterization. The instrument used was a commercially produced cuvette oximeter similar to that developed by Groom and Wood.

Comparisons of 190 cuvette oximeter recordings from 38 cases of suspected congenital heart disease were made with samples analyzed by a modification of the Roughton-Scholander microgasometric method for blood oxygen saturation.

The over-all standard deviation of the difference between the two determinations was 4.2 per cent. This error was influenced markedly by the poor agreement of the methods below gasometric saturations of 70 per cent. The standard deviation was 3.6 per cent in the range of gasometric saturations of 70 to 100 per cent, which included 145 of the 190 comparisons. The standard errors would appear excessive for the use of the cuvette oximeter values under the conditions of the study as substitutes for the gasometric analyses or for consideration of the values obtained as absolute determinations.

The use of the whole blood oximeter at the time

of cardiac catheterization provides information of value pertaining to (1) immediate presumptive diagnosis, (2) sampling from representative sites, (3) unusual locations of the catheter tip, and (4) basal state of the patient.

Under the conditions of the study, more accuracy was obtained in determining increments between blood oxygen saturations recorded successively by the cuvette oximeter than in determining absolute values. Of 17 cases where a diagnosis of arteriovenous shunt was made by gasometric analyses, 15 had given strong evidence by oximetry of shunts such as those later diagnosed. Only one case showed presumptive evidence of an arteriovenous shunt by oximetry who did not show evidence of a similar shunt by gasometric analyses.

Cuvette oximetry was a most useful adjunct to the technique of diagnostic cardiac catheterization.

MINTZ

McCahan, J. F.: Medicine Plus Industry Equals Occupational Health. New England J. Med. **247:** 470 (Sept. 25), 1952.

The author points out that the concept of health is gaining increased emphasis and that the practice of industrial medicine with the establishment of industrial health services affords an opportunity for the medical profession to become oriented to health as a positive concept through participation in the practice of preventive medicine. Well-developed small-plant industrial health services are needed particularly at this time. Preventive medical programs in industry are particularly needful of physicians with a real interest in the application of the principles of preventive medicine; early detection should be followed by elimination or modification of the personal and environmental factors which, if left uncontrolled, would probably lead to more serious illness or injury. The physician's role is planning a program and furnishing service—for these he requires knowledge and information, time, and the cooperation of his fellow practitioners, management, workers and the community at large.

ROSENBAUM

Swann, H. G., Prine, J. M., Moore, V., and Rice, R. D.: The Intrarenal Pressure during Experimental Renal Hypertension. J. Exper. Med. **96:** 281 (Oct.), 1952.

The intrarenal interstitial pressure was measured during the course of experimental renal hypertension in dogs. In perinephritic hypertension, produced by wrapping the kidney in a cellophane bag, the intrarenal pressure rose slowly to a level of about 60 mm. Hg. In the hypertension following partial occlusion of the renal artery by the Goldblatt technique, the intrarenal pressure remained approximately normal, except in malignant hypertension when it tended to decline to about 9 mm. Hg. In the Goldblatt hypertensives, the arterial clamp reduces renal blood flow; in compensation systemic pressure rises by humoral and perhaps other mechanisms. In the perinephritic hypertensives, the high intrarenal interstitial pressure, in effect, works to collapse all blood vessels. In order for blood flow to occur, renal intravascular pressures, therefore, must all exceed intrarenal pressure. The effective perfusion pressure is low, ischemia occurs and in compensation the systemic pressure rises by the same mechanisms as in Goldblatt hypertension. It is probable that the elevated intrarenal pressure imposes its resistance primarily at the junction of arcuate and interlobar veins. The two experimental hypertensions herein examined are considered as examples of influent resistance hypertensions and effluent resistance hypertensions, the former being due to renal arterial or arteriolar resistance and the latter due to renal venous resistance, specifically at the arcuate-interlobar junction.

BERNSTEIN

Talbot, T. J., and Silverman, J. J.: Asymptomatic Arteriovenous Fistula of the Lung. Arch. Int. Med. **90:** 569 (Oct.), 1952.

An arteriovenous fistula of the lung, successfully removed by surgery, is reported in an asymptomatic 48 year old man. In the differential diagnosis of a nodule in the lung, an arteriovenous fistula should be considered. An arteriovenous fistula may present itself solely as an isolated nodule in the lung parenchyma.

Laminagraphic studies are recommended whenever a pulmonary arteriovenous fistula is suspected. Abnormal vessels leading to and from the aneurysm may be identified by this technic. The symptoms and signs of pulmonary arteriovenous fistula vary widely. The absence of the diagnostic triad of polycythemia, clubbing of the fingers and toes, and cyanosis, as well as of other signs, in arteriovenous fistula is discussed.

BERNSTEIN

Miller, G., Goldberg, H., Elisberg, E. I., Snider, G. L., Toor, M., and Katz, L. N.: Cardiopulmonary Studies in Patients with Mitral Stenosis. I. Cardiovascular Dynamics. J. Lab. & Clin. Med. **40:** 390 (Sept.), 1952.

Cardiovascular dynamics were studied in 20 patients with mitral stenosis by means of right heart catheterization. At rest there was generally an increased mean pulmonary artery pressure, a reduced cardiac output, an increased pulmonary venous capillary (PVC) pressure, and an increased pulmonary arteriolar resistance. Generally there was a small rise in cardiac output on exercise associated with a marked rise in pulmonary artery pressure. Pulmonary infarction occurred in 4 of 10 patients, 8 to 36 hours after PVC pressures were taken at rest. On the basis of preliminary observations, surgery

was indicated in dynamically significant stenosis and when the disease appears to be progressive, unless there is present some specific contraindication.

In view of the beneficial effects frequently observed after valvulotomy in patients with mitral stenosis, every patient with this lesion deserves particularly careful and frequent evaluation. The data obtained by cardiac catheterization studies are of great aid in such an evaluation.

MINTZ

Wagner, A., and Poindexter, C. A.: Esterification of Serum Cholesterol. I. Serial Determinations in Health. J. Lab. & Clin. Med. **40:** 321 (Sept.), 1952.

When serum is incubated at 37 C., the free cholesterol originally present gradually disappears, without change in the value for total cholesterol by means of a specific enzyme, cholesterol esterase.

The work reported here was undertaken to test the constancy of the esterifying power of the serum from time to time in the same individual.

The authors confirmed the existence of a cholesterol-esterifying reaction in incubating serum. They also presented evidence that the variation of the esterifying power of the serum within individuals is less than the variation among individuals. The esterifying power of the serum of any healthy individual fluctuates within a range that is inherent in the individual constitution. In a small group of middle aged individuals the esterifying power was both less active and less variable than it was in the younger group.

MINTZ

Wagner, A., and Rogalski, L.: Esterification of Serum Cholesterol. II. Influence of Phosphatide and Other Factors. J. Lab. & Clin. Med. **40:** 324 (Sept.), 1952.

The existence of a cholesterol-esterifying principle in blood has been confirmed and extended.

The authors discovered that when normal serum is incubated in contact with a glaze of melted C. P. cholesterol (melting point 149 C.), the esterification which would otherwise occur in the serum is either inhibited or reversed. They also found that the addition to healthy serum, before incubation, of a mixture of soybean phosphatides, regularly results in an increase of cholesterol esterification. The speed of the reaction is increased and a new equilibrium is established. The phosphatide effect depends upon the coexistence of a heat-labile component of serum. It is independent of emulsifying characteristics and within limits it is quantitative. The phosphatide effect is lost in the presence of extrinsic cholesterol.

MINTZ

Wagner, A., and Rogalski, L.: Esterification of Serum Cholesterol. III. In Hypercholesterolemic Rabbits. J. Lab. & Clin. Med. **40:** 334 (Sept.), 1952.

This work is concerned with the comparative behavior of cholesterol that has been added to rabbit serum by feeding.

All the rabbits showed a fairly uniform cholesterol esterifying ability in the serum before cholesterol feeding. The production of hypercholesterolemia changed this characteristic quantitatively in an unpredictable fashion and sometimes qualitatively, producing reversal or hydrolysis. The results could not be correlated with the initial or the final cholesterol concentrations or the initial or final combined: free ratios or the absolute increments of free cholesterol during the feeding period.

During the cholesterol feeding the esterified cholesterol reaches disproportionately greater heights in vivo than does the free fraction. Lack of correlation between this finding and the alterations in the esterifying ability of the serum suggest that the synthesizing cholesterol esterase present in the serum is not primary in the regulation of the serum cholesterol partition of hypercholesterolemic rabbits.

MINTZ

Shearer, M. C., Sikkema, S. H., and Holden, S. W.: Prevalence of Heart Disease in University Students. Am. J. Pub. Health **42:** 1103 (Sept.), 1952.

A survey of 3,645 entering students was made at the University of Colorado. Normal hearts were found in 96.5 per cent of the students. Physiologic murmurs were heard in 13.5 per cent with a greater incidence in women than in men. Organic heart disease was present in 1.2 per cent. Congenital heart disease was diagnosed in 0.5 per cent. Rheumatic heart disease was found in 0.7 per cent. A history of rheumatic infection was given by 2.6 per cent and of those cases one-fourth had demonstrable valve lesions. Growing pains were reported more frequently by the women than by the men. In this student group there was no significant difference in the rate of incidence of previous rheumatic infection among the residents and nonresidents of Colorado.

BERNSTEIN

AMERICAN HEART ASSOCIATION, INC.

44 East 23rd Street, New York 10, N.Y.

Telephone Gramercy 7-9170

ASSOCIATION FELLOWSHIPS AND GRANTS

Applications for Research Fellowships and Established Investigatorships for the 1954–55 fiscal year must be received by Sept. 15, 1953. Applications for research grants-in-aid may be filed up to Dec. 1, 1953. Information and forms may be obtained from the Association's Medical Director.

NEW CAREER INVESTIGATORS

The Association has awarded Career Investigatorships to two faculty members of the Harvard Medical School, John R. Pappenheimer, Ph.D., Visiting Professor of Physiology, and Albert H. Coons, M.D., Visiting Professor of Bacteriology and Immunology.

The latest appointments bring to three the number of Career Investigators being supported by the Association throughout their productive careers. Victor Lorber, M.D., Ph.D., who was named as the Association's first Career Investigator in 1951, is now conducting studies of chemical processes within the heart muscle at the University of Minnesota.

Dr. Pappenheimer, 37 years of age, has centered his recent investigations on the subject of capillary permeability. These studies have provided a better understanding of the effectiveness of blood replacement by transfusion or by the use of blood substitutes in cases of anemia and shock. Dr. Pappenheimer is also seeking new methods for studying the various mechanisms concerned in the regulation of blood flow. During World War II, Dr. Pappenheimer worked on the development of oxygen equipment for high altitude flying in military aviation.

Dr. Coons, 41, has been working in the field of disease immunity, and his studies have been followed with great interest because of the possibility that they may throw new light on the mechanisms of rheumatic fever. Among his major contributions is the development by Dr. Coons and his associates since 1940 of a new tracer technic using the brightly fluorescent dye, fluorescein, for studying the distribution, interaction, and characteristics of antigens and antibodies in the animal body. When identified with fluorescein, antibodies may be observed to adhere to tissue cells containing antigen. A distinctly yellow-green color is produced when the cells are illuminated with ultraviolet light under the microscope. Using a variation of this method, Dr. Coons has added to the evidence that antibodies are produced by plasma cells present in lymph nodes and spleen. The discovery of this technic and its use has important applications to the entire field of infectious diseases and immunology. It is considered especially promising in regard to studies of the possible mechanisms involved in rheumatic fever, since many investigators have long suspected that the rheumatic process represents some sort of tissue response to antigen-antibody reaction.

Dr. Pappenheimer joined the faculty of Harvard Medical School in 1946 and became Assistant Professor of Physiology in 1949. He became Visiting Professor on taking over his Career Investigatorship. Dr. Pappenheimer was born in New York City. He received his B.S. degree from Harvard in 1936 and his Ph.D. from Cambridge University in England in 1940. He has been an instructor at Univer-

ity College, London, and at the College of Physicians and Surgeons, New York, and a Fellow in Biophysics of the Johnson Foundation, University of Pennsylvania.

Dr. Coons began his investigations as a National Research Council Fellow at Harvard in 1940. After service with the U. S. Army Medical Corps with the 105th General Hospital in Australia and New Guinea during World War II, Dr. Coons returned to Harvard in 1946. He became Silas Arnold Houghton Assistant Professor in 1950. A native of Gloversville, N. Y., he received his A.B. degree from Williams College in 1933 and his M.D. cum laude from Harvard in 1937. He served as a house officer at the Massachusetts General Hospital and as assistant resident physician and research fellow at the Thorndike Memorial Laboratory of the Boston City Hospital.

The Career Investigatorships, unique in the field of research support, make it possible for the investigators to devote themselves almost exclusively to their research interests, without restriction by the terms of the award. The investigators are chosen for their interest and accomplishments in fundamental research which directly or indirectly add to cardiovascular knowledge. The Career Investigator is freed from excessive administrative and teaching assignments and is required to devote at least 85 per cent of his time to research of his own choosing. He may work at any institution he selects. The Association makes annual awards of $25,000 to cover each Investigator's salary, assistance and supplies.

FIVE-YEAR TOTAL OF RESEARCH AWARDS

With the award of two new Career Investigatorships, the Association has completed the fifth year of its national research support program. During the five-year period the Association and its affiliates have awarded a grand total of almost six and a half million dollars to fundamental and applied studies in the cardiovascular field. These awards have been made possible by public contributions to the annual Heart Fund campaigns.

In the past fiscal year, the American Heart Association and its affiliates appropriated a total of $810,830.59 for 142 fellowships and grants. This sum provided for three Career Investigators, twenty Established Investigators, thirty Research Fellows, and eighty-nine Grants-in-Aid. In addition to their participation in financing the national joint research awards, many affiliated state and local Heart Associations make separate research awards in their respective areas. It is estimated that research awards by affiliates and their chapters during the past fiscal year totaled approximately one and a quarter million dollars, making a combined total, with the national awards, of more than two million dollars for the year. Fifty per cent of the total funds available to the National Office each year are allocated to the national research program.

HEART MODELS

Two new models have been added to the previous series of ten life-size rubber reproductions of normal and diseased hearts developed by the Association for use as visual aids in medical teaching. One of the new models demonstrates patent ductus arteriosus, and the other, coarctation of the aorta. Each model in the series can be fitted into a base which is a model of the human diaphragm.

Originally supplied only in the natural color of latex rubber, the models are now available either unpainted or painted with fluorescent pigment in several colors. This simplifies the identification of the different chambers and blood vessels. The painting is being done by handicapped workers, through arrangement with the Brooklyn Bureau of Social Service.

A detailed price list follows:

	Unpainted	*Painted*
Set of models with one diaphragm	$180.00	$234.00
Set of 10 models with one diaphragm	150.00	195.00
Single Models (each)	16.50	21.50
Diaphragm bases (each)	6.00	

Packing and shipping charges are additional. Those possessing unpainted sets who desire to have them painted may do so by returning them to the American Heart Association at 44 East 23rd Street, New York 10, N. Y., with a check to cover the difference in cost.

Approximately one month is required for delivery of new or repainted sets.

CARDIOVASCULAR AWARDS AT AMA CONVENTION

Four out of six medals awarded to scientific exhibits at the American Medical Association convention in June were won by exhibits in the cardiovascular field, including both gold medals presented. The Billings Gold Medal for "excellence of correlated facts and presentation" was awarded to J. Scott Butterworth, M.D., Charles A. Poindexter, M.D., and C. E. Peterson of New York University Post-Graduate Medical School, and the American Heart Association for a joint exhibit entitled "The Cardiac Silhouette." This exhibit comprised units known as fluorodemonstrators which provide viewers with an opportunity to study the distinctive features of the heart as they appear to the doctor during x-ray or fluoroscopic examination of the living patient. Using special lighting effects and the Association's heart models described above, the apparatus simulates the shadows cast by the living heart on a fluoroscope screen.

The Hektoen Gold Medal was awarded to Oscar V. Batson, M.D., University of Pennsylvania Graduate School for Medicine, for an exhibit on "The Anatomy of Veins."

The Hektoen Bronze Medal was presented to F. D. Dodrill, M.D., and his associates, Harper Hospital, Detroit, for an exhibit, "Exposure of the Pulmonary and Mitral Valves in Living Patients with the Aid of the Mechanical Heart." Research leading to the development of this mechanical heart has been supported by the Michigan Heart Association, an affiliate of the American Heart Association.

T. J. Dry, M.D., and associates, Mayo Clinic, Rochester, Minn., won the Billings Silver Medal for an exhibit, "Diseases of the Mitral Valve—Diagnosis and Surgical Treatment."

Two investigators whose research work is currently being supported by awards from the American Heart Association also won recognition in the Section awards presented by the American Medical Association. One was Charles P. Bailey, M.D., Hahnemann Medical College, Philadelphia, who, with his associates, won a Certificate of Merit in the Section on Diseases of the Chest for "The Role of Hypothermia in Cardiac Surgery." Another Certificate of Merit, in the Section on Experimental Medicine and Therapeutics, was awarded to William Dameshek, M.D., and Mario Stefanini, M.D., New England Center Hospital, Boston, for "The Blood Platelets and Idiopathetic Thrombocytopenic Purpura." Dr. Stefanini holds an AHA Established Investigatorship for 1953–54.

Other Sections awards in the cardiovascular field included:

Section on Internal Medicine: Honorable Mention to Harry Mandelbaum, M.D., and Robert A. Mandelbaum, M.D., Jewish Hospital of Brooklyn and Jewish Sanitarium and Hospital for Chronic Diseases, Brooklyn for an exhibit on Clinical Ballistocardiography;

Section on General Practice: Honorable Mention to Jacob J. Silverman, M.D., and Harold B. Trachtenberg, M.D., Staten Island Hospital, Staten Island, N. Y., for an exhibit on "Hazards of Mercurial Diuretics";

Section on Radiology: Certificate of Merit to Fay A. LeFevre, M.D., and associates, Cleveland Clinic, Cleveland, for an exhibit on "Diagnosis of Aorta-Iliac Artery Occlusion"; also, Honorable Mention to Melvin M. Figley, M.D., University Hospital, Ann Arbor, Mich., for "Accessory Roentgen Signs of Coarctation of the Aorta";

Section on Surgery, General and Abdominal: Certificate of Merit to O. T. Clagett, M.D., and associates, Mayo Clinic, Rochester, Minn., for an exhibit on "Coarctation of the Aorta—Diagnosis and Surgical Treatment."

In addition, the American Medical Association's highest scientific honor, the Distinguished Service Medal, was awarded to Alfred Blalock, M.D., Johns Hopkins Hospital, Baltimore, whose contributions to heart and vascular surgery are well known. Dr. Blalock is a member of the Founders Group of the American Heart Association's Scientific Council.

"NOMENCLATURE AND CRITERIA"

The recently published Fifth Edition of *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Blood Vessels* con-

tains many new illustrations and a great deal of new material, according to a statement issued by Harold E. B. Pardee, M.D., Chairman, Criteria Committee of the New York Heart Association, which has been responsible for the preparation of all five editions of this standard medical handbook. It may be purchased through Heart Associations or medical bookstores at $4.95 a copy.

For this edition, Dr. Pardee said, "the former text of each section was reviewed by the appropriate subcommittee and rewritten as necessary in the light of the advances of knowledge." Thirty-eight physicians served on these subcommittees. When revised, the sections of the book were reviewed by the Criteria Committee sitting as a jury, Dr. Pardee added, "and further changes were made when necessary in conformity with the general plan as outlined. The rewritten sections on roentgenology, electrocardiography and pathology, and the new section on peripheral vascular diseases were reviewed by the Chairman of the Criteria Committee in consultation with the Chairman of the particular subcommittee."

The first edition of *Nomenclature and Criteria* was published in 1929; the fourth, the latest preceding the current volume, appeared in 1939. The original purpose of the book, according to Dr. Pardee, "was to unify and standardize the nomenclature used for the diagnosis of diseases of the heart and great vessels. Different terms were often used by different people to describe the same cardiac disease and it was hoped to set up a standard nomenclature—a list of titles—that would be universally used and would make for increased clarity of expression and understanding."

The criteria themselves have been selected with special attention to established stability of their diagnostic importance, Dr. Pardee declared, and for the most part include only those features "whose presence was considered absolutely necessary to establish the diagnosis concerned." The many new criteria which appear in this edition "have graduated into the tried and proved category," he pointed out, emphasizing that "new and untested features are omitted even though they may show promise of future importance."

SCIENTIFIC PROGRAM OF SECTION ON CLINICAL CARDIOLOGY

The Section on Clinical Cardiology of the American Heart Association will sponsor a two-day scientific program at the Conrad Hilton Hotel in Chicago on April 3 and 4, 1954. This program will constitute a portion of the Annual Meeting of the American Heart Association and will immediately precede the Annual Sessions of the American College of Physicians. The meeting will be open to all members of the medical profession. Wright R. Adams, M.D., Chicago, is Chairman of the Program Committee. Members of the American Heart Association who wish to present papers should send a 250 to 300 word abstract of the proposed paper to Charles D. Marple, M.D., Medical Director, American Heart Association, 44 East 23rd Street, New York 10, New York. *All papers should be on subjects of distinct clinical interest. The deadline for the receipt of abstracts is Jan. 1, 1954.*

REGIONAL CONFERENCES

Seven regional conferences will be held by the Association in the fall for Board, Committee and staff representatives of affiliated Heart Associations and their chapters throughout the country. At these conferences, physicians active in the Association will join with lay representatives and representatives from the National Office in planning Heart programs which will effectively meet the varying needs in different sections of the United States.

The tentative schedule of conferences follows: Providence, R. I., Sept. 16 and 17; Detroit, Sept. 23 and 24; Salt Lake City, Sept. 23 and 24; Kansas City, Mo., Sept. 30 and Oct. 1; San Francisco, Oct. 1 and 2; Birmingham, Ala., Oct. 7 and 8; Wilmington, Del., Oct. 21 and 22.

RESEARCH FELLOWSHIPS OF AMERICAN COLLEGE OF PHYSICIANS

The American College of Physicians announces that a limited number of Fellowships in Medicine will be available from July 1, 1954 to June 30, 1955. These Fellowships are designed to provide an opportunity for re-

search training either in the basic medical sciences or in the application of these sciences to clinical investigation. They are for the benefit of physicians who are in the early stages of their preparation for a teaching and investigative career in Internal Medicine. The stipend will be from $3,000 to $3,500. Application forms may be obtained from The American College of Physicians, 4200 Pine Street, Philadelphia 4, and must be submitted in duplicate not later than Oct. 1, 1953. Announcement of awards will be made in November 1953.

FULBRIGHT AWARDS

Fulbright Awards are available for university lecturing and postdoctoral-level research in Europe, the Near East, Japan and Pakistan during 1954–55. The Fulbright grants were established by the Seventy-Ninth Congress as part of the educational exchange program to promote better mutual understanding between the United States and other countries. The closing date for applications is October 15, 1953. Application forms and additional information may be obtained from the Conference Board of Associated Research Councils, Committee on International Exchange of Persons, 2101 Constitution Avenue, Washington 25, D. C.

SYMPOSIUM AND SEMINARS

The University of Vermont, in conjunction with the Vermont and New Hampshire Heart Associations, will hold an informal International Symposium on "Cardiovascular Regulations" at Burlington, Vt., Sept. 8 through 10. Papers will be presented by speakers from Egypt, Argentina, Chile, England, Sweden and Germany. Sessions will take place at Oakledge Manor, a hotel located on the shore of Lake Champlain, near Burlington.

The Symposium will be followed by two Cardiac Seminars, arranged by the Division of Experimental Medicine at the University of Vermont College of Medicine and sponsored by the Vermont Heart Association. The Seminars will be held in Burlington Sept. 10 through 12. The first, in two parts, "The Normal Electrocardiogram" and "Electrocardiographic Diagnosis of Myocardial Infarction," will be presented by E. Lepeschkin, M.D., University of Vermont; H. B. Levine, M.D., Harvard University, and C. E. Kossmann, M.D., New York University. There will be a fee of $10.00. The second Seminar, "Hormonal and Neurogenic Factors in Cardiac Pathology and Therapy," will be presented by W. Raab, M.D., University of Vermont. There will be a fee of $5.00. Additional information may be obtained from W. Raab, M.D., or E. Lepeschkin, M.D., University of Vermont, Burlington.

MINNESOTA SYMPOSIUM

Under the auspices of the Minnesota Heart Association, the University of Minnesota, Minneapolis, will present a Symposium on Cardiovascular Physiology and Surgery from Sept. 14 to 16, in which many internationally known physiologists and vascular surgeons will participate. The Symposium will be open, without fee, to all physicians and to qualified investigators in the field of cardiac physiology. Further information may be obtained from Robert B. Howard, M.D., Director, Department of Continuation Medical Education, University of Minnesota Hospital, Minneapolis 14.

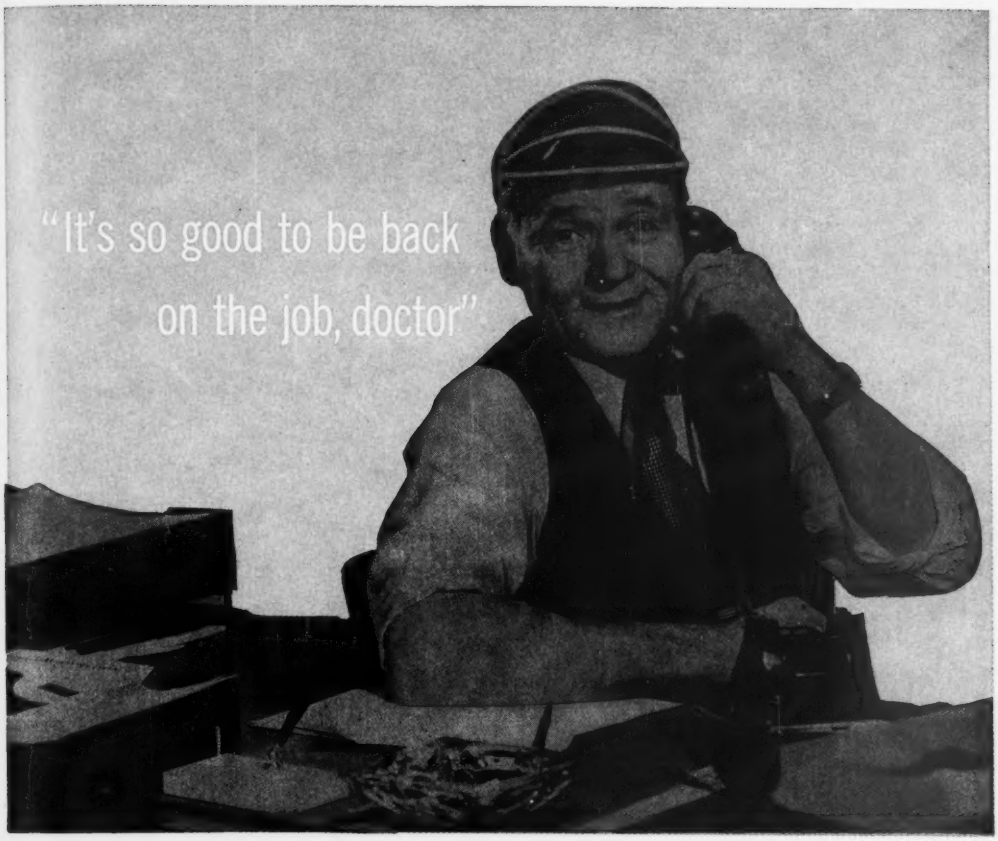
MEETINGS

Sept. 8–12: International Congress of the European Society of Haematology, Amsterdam, Holland. M. C. Verloop, M.D., Secretary, Maliesingle 15, Utrecht, Holland.

Sept. 18–20: Congress of the International Society of Angiology, Lisbon, Portugal. Henry Haimovici, M.D., Secretary, 105 East 90th Street, New York 28.

Oct. 6–9: American Academy of Pediatrics, annual meeting, Municipal Auditorium, Miami, Fla. E. H. Christopherson, M.D., Executive Secretary, 610 Church Street, Evanston, Ill.

Nov. 1–2: American Society for the Study of Arteriosclerosis; Hotel Knickerbocker, Chicago. Louis N. Katz, M.D., Program Chairman, Michael Reese Hospital, Chicago 16.



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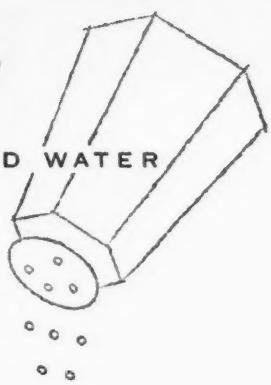

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Circulation

AUGUST 1953
VOL. VIII NO. 2

A JOURNAL of the AMERICAN HEART ASSOCIATION

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